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The Current Status of WHO Group 3 Pulmonary Hypertension

Pulmonary Hypertension and Chronic Obstructive Pulmonary Disease: When Is it Out of Proportion?
Sonja Bartolome, MD, FCCP

Pulmonary Hypertension in Idiopathic Pulmonary Fibrosis
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Ask the Expert: When Is Testing Beyond Overnight Oximetry Indicated for Assessment of Sleep-Disordered Breathing in Pulmonary Arterial Hypertension?
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The mission of the Scientific Leadership Council is to provide medical and scientific guidance and support to the PHA for:

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Advances in Pulmonary Hypertension
Official Journal of the Pulmonary Hypertension Association

General Information
Advances in Pulmonary Hypertension: Official Journal of the Pulmonary Hypertension Association is a quarterly publication directed by an editorial board of renowned experts with the oversight of the Association’s Scientific Leadership Council. Its mission is to help physicians in their clinical decision making by informing them of important trends affecting their practice and providing an analysis of the impact of new findings and current information in the peer-reviewed literature. Each article is reviewed and approved by members of the Editorial Advisory Board.

While most articles are invited by the editorial board, the following submissions will be considered for publication:
• Reviews that summarize and synthesize peer-reviewed literature to date on relevant topics
• Letters to the Editor
• Clinical case studies

Submitted manuscripts are reviewed by the editorial board and other experts in the field. Acceptance of manuscripts is determined by factors such as quality, relevance, and perceived value to clinical decision making.

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Submissions should be sent via e-mail as an attached Word document to the Editor-in-Chief, Myung Park, MD, at mpark@medicine.umaryland.edu. Manuscripts should be double-spaced and follow AMA style. Full-length manuscripts should not exceed 4,000 words including references. References should be limited to 50 entries. No more than 5 figures should accompany the manuscript. Acceptable file formats are .gif, .tif, and .jpg. Each figure should be a separate file and figure legends should appear at the end of the manuscript. Tables should be self-explanatory and details of the table should not be repeated in the manuscript. Tables should be prepared as part of the Word document. No more than 3 tables should be included with the manuscript. References should conform to AMA style and be numbered consecutively in the text. Reference numbers should be placed in parentheses at the end of the relevant sentence. Accepted manuscripts will be edited for clarity, spelling, punctuation, grammar, and consistency with AMA style.

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Authors should be certain to include the following with the manuscript:
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3. Copyright release form signed by all authors
4. Conflict of Interest forms for all authors
5. List of approximately 5 key words for indexing purposes
6. Summary of the paper not exceeding 250 words in the format of Background; Objectives; Summary/Conclusions

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Pulmonary Hypertension Due to Lung Disease: Between a Rock and a Hard Place

Pulmonary hypertension due to lung disease (Group 3 PH) represents one of the most challenging subsets of PH patients to evaluate and manage. Being afflicted by progressive severe lung disease compounded by PH places 3 strikes against the patient with dysfunctions in parenchyma and/or airway, pulmonary vasculature, and right heart function. Thus, we often hear desperation in the voices of patients struggling with severe Group 3 PH, when each breath taken becomes an act of labor.

These patients are often referred to PH centers in the hopes that pulmonary arterial hypertension (PAH) therapies can help them to improve the quality of their lives. Unfortunately, the presence of significant lung disease often poses both diagnostic and therapeutic challenges. It has been well established that echocardiograms are not very reliable as screening tools in patients with lung disease. Furthermore, accurate interpretation of hemodynamics with right heart catheterization usually requires additional scrutiny due to the effects from wide intrathoracic pressure changes.

As for treatment considerations, there is a strong desire to see if a patient would benefit from “off-label” use of pulmonary vasodilators. However, this group of patients is challenged because pulmonary vasodilators can worsen their hypoxia and clinical status due to underlying lung disease, and for many, there are no effective disease modifying treatments for most chronic pulmonary disorders. On the other hand, there are reports of carefully selected patients with significant pulmonary arterial vasculopathy and right heart dysfunction in the presence of lung disease responding to PAH treatments, causing us to question whether this disease process is a single or separate entity.

So it is with sincere pleasure that I present this issue of Advances, which focuses on the current status of Group 3 PH: covering questions yet to be answered, and pitfalls to avoid. I am sincerely grateful to our guest editor Dr Jeffrey Edelman for proposing the topic of Group 3 PH for this issue, and bringing together a distinguished group of experts to share their insights on this disease state—from an in-depth discussion of the pathophysiology of hypoxic pulmonary vascular disease to the impact of PH with underlying lung diseases such as COPD and pulmonary fibrosis. The Roundtable participants, led by Dr Edelman and joined by Drs Klinger, Levine, and Schilz, accurately articulate the difficulties in managing Group 3 PH. I hope you find the information in this issue helpful in caring for your patients.

Myung H. Park, MD
Associate Professor of Medicine
Director, Pulmonary Vascular Disease Program
University of Maryland School of Medicine

(Continued on page 158)
INDICATIONS

- Adempas (riociguat) tablets is indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class.
- Adempas is indicated for the treatment of adults with pulmonary arterial hypertension (PAH), (WHO Group 1), to improve exercise capacity, WHO functional class and to delay clinical worsening.

For more information visit Adempas-US.com.

IMPORTANT SAFETY INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

Do not administer Adempas (riociguat) tablets to a pregnant female because it may cause fetal harm.

Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception.

For all female patients, Adempas is available only through a restricted program called the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program.

Contraindications

Adempas is contraindicated in:
- Pregnancy. Adempas may cause fetal harm when administered to a pregnant woman. Adempas was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.
- Co-administration with nitrates or nitric oxide donors (such as amyl nitrite) in any form.
- Concomitant administration with phosphodiesterase (PDE) inhibitors, including specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline).

Warnings and Precautions

Embryo-Fetal Toxicity. Adempas may cause fetal harm when administered during pregnancy and is contraindicated for use in women who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, advise use of acceptable contraception and obtain monthly pregnancy tests. For females, Adempas is only available through a restricted program under the Adempas REMS Program.

Adempas REMS Program. Females can only receive Adempas through the Adempas REMS Program, a restricted distribution program. Important requirements of the Adempas REMS program include the following:
- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the Adempas REMS Program prior to initiating Adempas. Male patients are not enrolled in the Adempas REMS Program.
- Female patients of reproductive potential must comply with the pregnancy testing and contraception requirements.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive Adempas.

Further information, including a list of certified pharmacies, is available at www.AdempasREMS.com or 1-855-4ADEMPAS.

Hypotension. Adempas reduces blood pressure. Consider the potential for symptomatic hypotension or ischemia in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, or concomitant treatment with antihypertensives or strong CYP and P-gp/BCRP inhibitors. Consider a dose reduction if patient develops signs or symptoms of hypotension.

Bleeding. In the placebo-controlled clinical trials program, serious bleeding occurred in 2.4% of patients taking Adempas compared to 0% of placebo patients. Serious hemoptysis occurred in 5 (1%) patients taking Adempas compared to 0 placebo patients, including one event with fatal outcome. Serious hemorrhagic events also included 2 patients with vaginal hemorrhage, 2 with catheter site hemorrhage, and 1 each with subdural hematoma, hematemesis, and intra-abdominal hemorrhage.

Pulmonary Veno-Occlusive Disease. Pulmonary vasoconstrictors may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Therefore, administration of Adempas to such patients is not recommended. Should signs of pulmonary edema occur, the possibility of associated PVOD should be considered and if confirmed, discontinue treatment with Adempas.

Most Common Adverse Reactions

The most common adverse reactions occurring more frequently (≥3%) on Adempas than placebo were headache (27% vs 18%), dyspepsia/gastritis (21% vs 8%), dizziness (20% vs 13%), nausea (14% vs 11%), diarrhea (12% vs 8%), hypotension (10% vs 4%), vomiting (10% vs 7%), anemia (7% vs 2%), gastroesophageal reflux disease (5% vs 2%), and constipation (5% vs 1%).

Other events that were seen more frequently in Adempas compared to placebo and potentially related to treatment were: palpitations, nasal congestion, epistaxis, dysphagia, abdominal distension and peripheral edema.

For additional important risk and use information, please see brief summary of full Prescribing Information on adjacent page.
Adempas (riociguat) tablets, for oral use

Initial U.S. Approval: 2013

BRIEF SUMMARY of prescribing information

CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

Do not administer Adempas to a pregnant female because it may cause fetal harm (see Contraindications (4) and Use in Specific Populations (8.1)). Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception (see Use in Specific Populations (8.1)). For all female patients, Adempas is available only through a restricted program called the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program (see Warnings and Precautions (5.2)).

1 INDICATIONS AND USAGE

1.1 Chronic-Thromboembolic Pulmonary Hypertension

Adempas is indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class (see Clinical Studies (14.1)).

1.2 Pulmonary Arterial Hypertension

Adempas is indicated for the treatment of adults with pulmonary arterial hypertension (PAH), (WHO Group 1), to improve exercise capacity, WHO functional class, and to delay clinical worsening. Efficacy was shown in patients on Adempas monotherapy or in combination with endothelin receptor antagonists or prostanoids. Studies establishing efficacy included predominantly patients with WHO functional class II–III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%) (see Clinical Studies (14.2)).

4 CONTRAINDICATIONS

4.1 Pregnancy

Adempas may cause fetal harm when administered to a pregnant woman. Adempas is contraindicated in females who are pregnant. Adempas was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus (see Use in Specific Populations (8.1)).

4.2 Nitrates and Nitric Oxide Donors

Co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrate) in any form is contraindicated (see Drug Interactions (7.1), Clinical Pharmacology (12.2)).

4.3 Phosphodiesterase Inhibitors

Concomitant administration of Adempas with phosphodiesterase (PDE) inhibitors, including specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline) is contraindicated (see Drug Interactions (7.1), Clinical Pharmacology (12.2)).

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

Adempas may cause fetal harm when administered during pregnancy and is contraindicated for use in women who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, advise use of acceptable contraception and obtain monthly pregnancy tests. For females, Adempas is only available through a restricted program under the Adempas REMS Program (see Dosage and Administration (2.9), Warnings and Precautions (5.2) and Use in Specific Populations (8.1, 8.6)).

5.2 Adempas REMS Program

Females can only receive Adempas through the Adempas REMS Program, a restricted distribution program (see Warnings and Precautions (5.1)). Important requirements of the Adempas REMS Program include the following:

• Prescribers must be certified with the program by enrolling and completing training.
• All females, regardless of reproductive potential, must enroll in the Adempas REMS Program prior to initiating Adempas. Male patients are not enrolled in the Adempas REMS Program.
• Female patients of reproductive potential must comply with the pregnancy testing and contraception requirements (see Use in Specific Populations (8.6)).
• Pharmacies must be certified with the program and must only dispense to pharmacies authorized to receive Adempas.

Further information, including a list of certified pharmacies, is available at www.AdempasREMS.com or 1-855-4 ADEMPS.

5.3 Hypotension

Adempas reduces blood pressure. Consider the potential for symptomatic hypotension or ischemia in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, or concomitant treatment with antihypertensives or strong CYP and P-gp/BCRP inhibitors (see Drug Interactions (7.2), Clinical Pharmacology (12.3)). Consider a dose reduction if patient develops signs or symptoms of hypotension.

5.4 Bleeding

In the placebo-controlled clinical trials program, serious bleeding occurred in 2.4% of patients taking Adempas compared to 0.0% of placebo patients. Serious hemoptysis occurred in 5 (1%) patients taking Adempas compared to 0 placebo patients, including one event with fatal outcome. Serious hemorrhagic events also included 2 patients with vaginal hemorrhage, 2 with catheter site hemorrhage, and 1 each with subdural hematoma, hematemesis, and intra-abdominal hemorrhage.

5.5 Pulmonary Veno-Occclusive Disease

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Therefore, administration of Adempas to such patients is not recommended. Should signs of pulmonary edema occur, the possibility of associated PVOD should be considered and, if confirmed, discontinue treatment with Adempas.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

• Embryo-Fetal Toxicity (see Warnings and Precautions (5.1))
• Hypotension (see Warnings and Precautions (5.3))
• Bleeding (see Warnings and Precautions (5.4))

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflect exposure to Adempas in two, randomized, double blind, placebo-controlled trials in patients with irreversible or recurrent/persistent CTEPH (CHEST-1) and treatment naive or pre-treated PAH patients (PATENT-1). The population (Adempas: n = 490; Placebo: n = 214) was between the age of 18 and 80 years (see Clinical Studies (14.1, 14.2)).

The safety profile of Adempas in patients with irreversible or recurrent/persistent CTEPH (CHEST-1) and treatment naive or pre-treated PAH (PATENT-1) were similar. Therefore, adverse drug reactions (ADRs) identified from the 12 and 16 week placebo-controlled trials for PAH and CTEPH respectively were pooled, and those occurring more frequently on Adempas than placebo (≥3%) are displayed in Table 1 below. Most adverse events in Table 1 can be ascribed to the vasodilatory mechanism of action of Adempas.

The overall rates of discontinuation due to an adverse event in the pivotal placebo-controlled trials were 2.9% for Adempas and 5.1% for placebo (pooled data).

Table 1: Adverse Reactions Occurring More Frequently (≥3%) on Adempas than Placebo

(Pooled from CHEST 1 and PATENT 1)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Adempas % (n=490)</th>
<th>Placebo % (n=214)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>27</td>
<td>18</td>
</tr>
<tr>
<td>Dyspepsia and Gastroitis</td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td>Dizziness</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>Nausea</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Hypotension</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Anemia (including laboratory parameters)</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

Other events that were seen more frequently in riociguat compared to placebo and potentially related to treatment were: palpitations, nasal congestion, epistaxis, dysphagia, abdominal distension and peripheral edema. With longer observation in uncontrolled long-term extension studies the safety profile was similar to that observed in the placebo controlled phase 3 trials.

7 DRUG INTERACTIONS

7.1 Pharmacodynamic Interactions with Adempas

Nitrates: Co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrate) in any form is contraindicated because of hypotension (see Contraindications (4.1), Clinical Pharmacology (12.2)).

PDE Inhibitors: Co-administration of Adempas with phosphodiesterase (PDE) inhibitors, including specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) and nonspecific PDE inhibitors (such as dipyridamole or theophylline), is contraindicated because of hypotension (see Contraindications (4.3), Clinical Pharmacology (12.2)).

7.2 Pharmacokinetic Interactions with Adempas

Smoking: Plasma concentrations in smokers are reduced by 50-60% compared to nonsmokers. Based on pharmacokinetic modeling, for patients
who are smokers, doses higher than 2.5 mg three times a day may be considered in order to match exposure seen in nonsmoking patients. Safety and effectiveness of Adempas doses higher than 2.5 mg three times a day have not been established. A dose reduction should be considered in patients who stop smoking [see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)].

Strong CYP and P-gp/BCRP inhibitors: Concomitant use of riociguat with strong cytochrome CYP inhibitors and P-gp/BCRP inhibitors such as azole antymycotics (for example, ketoconazole, itraconazole) or HIV protease inhibitors (such as ritonavir) increase riociguat exposure and may result in hypotension. Consider a starting dose of 0.5 mg 3 times a day when initiating Adempas in patients receiving strong CYP and P-gp/BCRP inhibitors. Monitor for signs and symptoms of hypotension on initiation and on treatment with strong CYP and P-gp/BCRP inhibitors. A dose reduction should be considered in patients who may not tolerate the hypotensive effect of riociguat [see Dosage and Administration (2.5), Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)].

Strong CYP3A inducers: Strong inducers of CYP3A (for example, rifampin, phenytoin, carbamazepine, phenobarbital or St. John’s Wort) may significantly reduce riociguat exposure. Data are not available to guide dosing of riociguat when strong CYP3A inducers are co-administered [see Clinical Pharmacology (12.3)].

Antacids: Antacids such as aluminum hydroxide/magnesium hydroxide decrease riociguat absorption and should not be taken within 1 hour of taking Adempas [see Clinical Pharmacology (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

Risk Summary

Adempas may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. Adempas was teratogenic and embryotoxic in rats at doses with exposures approximately 3 times the human exposure. In rabbits, riociguat led to abortions at 5 times the human fetal toxicity at doses with exposures approximately 15 times the human exposure. If Adempas is used in pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus [see Contraindications (4.1)].

Animal Data

In rats administered riociguat orally (1, 5, 25 mg/kg/day) throughout organogenesis, an increased rate of cardiac ventricular-septal defect was observed at the highest dose tested. The highest dose produced evidence of maternal toxicity (reduced body weight). Post-implantation loss was statistically significantly increased from the mid-dose of 5 mg/kg/day. Plasma exposure at the lowest dose is approximately 0.15 times that in humans at the maximally recommended human dose (MRHD) of 2.5 mg three times a day based on area under the time-concentration curve (AUC). Plasma exposure at the highest dose is approximately 3 times that in humans at the MRHD while exposure at the mid-dose is approximately 0.5 times that in humans at the MRHD. In rabbits given doses of 0.5, 1.5 and 5 mg/kg/day, an increase in spontaneous abortions was observed starting at the middle dose of 1.5 mg/kg, and an increase in resorptions was observed at 5 mg/kg/day. Plasma exposures at these doses were 5 times and 15 times the human dose at MRHD respectively.

8.3 Nursing Mothers

It is not known if Adempas is present in human milk. Riociguat or its metabolites were present in the milk of rats. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from riociguat, discontinue nursing or Adempas.

8.4 Pediatric Use

Safety and effectiveness of Adempas in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of Adempas, 23% were 65 years of age and over, and 6% were 75 and over [see Clinical Studies (14)]. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Elderly patients showed a higher exposure to Adempas [see Clinical Pharmacology (12.3)].

8.6 Females and Males of Reproductive Potential

Pregnancy Testing: Female patients of reproductive potential must have a negative pregnancy test prior to starting treatment with Adempas, not during treatment, and one month after discontinuation of treatment with Adempas. Advise patients to contact their health care provider if they become pregnant or suspect they may be pregnant. Counsel patients on the risk to the fetus [see Boxed Warning and Dosage and Administration (2.2)].

Contraception: Female patients of reproductive potential must use acceptable methods of contraception during treatment with Adempas and for 1 month after treatment with Adempas. Patients may choose one highly effective form of contraception (intrauterine devices [IUD], contraceptive implants or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a partner’s vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider trained in contraceptive counseling [see Boxed Warning].

8.7 Renal Impairment

Safety and efficacy have not been demonstrated in patients with creatinine clearance <15 mL/min or on dialysis [see Clinical Pharmacology (12.3)].

8.8 Hepatic Impairment

Safety and efficacy have not been demonstrated in patients with severe hepatic impairment (Child Pugh C) [see Clinical Pharmacology (12.3)].

10 OVERDOSAGE

In cases of overdose, blood pressure should be closely monitored and supported as appropriate. Based on extensive plasma protein binding, riociguat is not expected to be dialyzable.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide). Embry-Fetal Toxicity

Instruct patients on the risk of fetal harm when Adempas is used during pregnancy [see Warnings and Precautions (5.1) and Use in Specific Populations (8.8)]. Instruct females of reproductive potential to use effective contraception and to contact her physician immediately if they suspect they may be pregnant. Female patients must enroll in the Adempas REMS Program.

Adempas REMS Program

For female patients, Adempas is available only through a restricted program called the Adempas REMS Program [see Warnings and Precautions (5.2)]. Male patients are not enrolled in the Adempas REMS Program.

Inform female patients (and their guardians, if applicable) of the following important requirements:

• All female patients must sign an enrollment form.
• Advise female patients of reproductive potential that she must comply with the pregnancy testing and contraception requirements [see Use in Specific Populations (8.6)].
• Educate and counsel females of reproductive potential on the use of emergency contraception in the event of unprotected sex or contraceptive failure.
• Advise pre-pubertal females to report any changes in their reproductive status immediately to her prescriber.

Review the Medication Guide and REMS educational materials with female patients.

Other Risks Associated with Adempas

• Inform patients of the contraindication of Adempas with nitrates or nitric oxide donors or PDE-5 inhibitors.
• Advise patients about the potential risks/signs of hemoptysis and to report any potential signs of hemoptysis to their physicians.
• Instruct patients on the dosing, titration, and maintenance of Adempas.
• Advise patients regarding activities that may impact the pharmacology of Adempas (strong multi pathway CYP inhibitors and P-gp/BCRP inhibitors and smoking). Patients should report all current medications and new medications to their physician.
• Advise patients that antacids should not be taken within 1 hour of taking Adempas.

Inform patients that Adempas can cause dizziness, which can affect the ability to drive and use machines [see Adverse Reactions (6.1)]. They should be aware of how they react to Adempas, before driving or operating machinery and if needed, consult their physician.

Manufactured for:

Bayer HealthCare Pharmaceuticals Inc.
Whippany, NJ 07981

Manufactured in Germany

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RACING TOWARD A CURE

June 20 - 22, 2014
JW Marriott Indianapolis
Indianapolis, Ind., U.S.A.

Registration opens January 2014
www.PHAssociation.org/Conference

Scientific Sessions:
New Treatments and Targets in Pulmonary Hypertension
At the Scientific Sessions, researchers and medical professionals will have the opportunity to engage in educational sessions about PH practice and cutting-edge research. This year’s topic, New Treatments and Targets in Pulmonary Hypertension, features PH experts who will share the latest developments in PH treatment and research. The Scientific Sessions will also feature a presentation of abstract posters and free-form panel discussions about the top abstracts.

Topics include:
• High Throughput Drug Screening in PAH: From Cells to People
• NOS Inhibition in COPD – Potential Therapeutics for Group III PH?
• Nitric Oxide Therapeutics in Pulmonary Vascular Disease
• Clinical Trial Design in Pulmonary Vascular Disease in Adults – Panel Discussion
• Metabolic Derangements in PH – Dichloracetate Studies
• Trials in Pediatric PH: Specific Concerns in Design and Endpoints
• Future Therapies in PAH – Update on the New Landscape and Drugs in the Pipeline
The Fundamentals of PH: Continuing Education Sessions
These sessions will take place throughout Conference and will focus on the essentials of PH treatment and include case-based learning on diagnosis and treatment.

Topics include:
- Classification, Screening and Diagnosis of PH
- Management of PAH: In With the Old and In With the New
- Follow-up in PAH: Clinical Measures or RV Imaging or Both?
- Etiology, Diagnosis, and Management of RV Failure in PH
- PH Associated with Connective Tissue Disease: Challenges in Diagnosis and Management
- PH in Lung Disease: Implications and Management

For a full list of topics, visit: www.PHAssociation.org/Conference/FundamentalsOfPH

Call for Abstracts and Case Studies
Researchers and clinicians are invited to submit abstracts in the areas of clinical science, basic science and case studies for a poster session at the International PH Conference and Scientific Sessions. Four abstracts will be selected for oral presentation at the Scientific Sessions and awards will be given for the top two abstracts. Summaries of top presentations will be published in a future issue of Advances in Pulmonary Hypertension. PHA encourages the submission of original abstracts; however, abstracts submitted to PHA do not need to be original work.

Submission Deadline: March 1, 2014

For more information on abstract submission or notification, visit: www.PHAssociation.org/Conference/Abstracts

For more information on PHA’s International PH Conference and Scientific Sessions:
Visit: www.PHAssociation.org/Conference
Call: 301-565-3004 | Email: Conference@PHAssociation.org
Research Room: Applications Now Accepted

PHA is accepting applications from researchers and institutions wishing to conduct research (patient surveys, cheek swabs, blood draws, etc.) during Conference. This event gives researchers the rare opportunity to collect data from the largest gathering of pulmonary hypertension patients in the world. At the last Conference in 2012, 180 attendees participated in the Research Room.

To submit an application for consideration, visit: www.PHAssociation.org/Conference/ResearchRoom

Questions? Contact ResearchRoom@PHAssociation.org or 301-565-3004 x 770.

Building Medical Education in PH

A Partnership Initiative to Advance Medical Understanding of Pulmonary Hypertension

Building Medical Education in PH (BME) events are designed to foster partnerships between PHA, PH Centers and medical professionals. The program supports continuing education in the PH field through CEU/CME educational events. Participating in PHA’s BME program can benefit your educational event by providing one-time use of PHA’s medical professionals mailing list, advertising support, educational materials for distribution to attendees and more.

To partner with PHA in Building Medical Education in PH for your upcoming CME event, please contact 301-565-3004 x776 or BME@PHAssociation.org.

To learn more about this partnership, visit: www.PHAssociation.org/BME

Upcoming BME events:

CTEPH: State of the Art 2014
A Multidisciplinary Symposium
Feb. 28–March 1, 2014
La Jolla, Calif.

7th International Conference on Neonatal and Childhood Pulmonary Vascular Disease
March 27–29, 2014
San Francisco, Calif.

The Alfred P. Fishman Symposium: New Treatment Approaches to Pulmonary Hypertension
April 26, 2014

1st Annual Drug Discovery and Development for Pulmonary Hypertension Symposium
July 14–15, 2014
Bethesda, Md.

To view a full list of educational opportunities for medical professionals, visit: www.PHAOnlineUniv.org/Calendar
ADCIRCA® (tadalafil) ONCE-DAILY CAN GIVE YOUR PATIENTS A SOLID FOUNDATION

A first-line PDE-5 inhibitor that can help improve exercise ability

• The only once-daily PDE-5 inhibitor for PAH

• 33-meter placebo-adjusted mean improvement in 6MWD at 16 weeks

• The most common adverse event with ADCIRCA (tadalafil) 40 mg is headache (42% ADCIRCA vs 15% placebo). Other common adverse events (reported by ≥9% of patients on ADCIRCA and more frequent than placebo by 2%) include myalgia (14% vs 4%), nasopharyngitis (13% vs 7%), flushing (13% vs 2%), respiratory tract infection (13% vs 6%), extremity pain (11% vs 2%), nausea (11% vs 6%), back pain (10% vs 6%), dyspepsia (10% vs 2%), and nasal congestion (9% vs 1%)1

• A $20 co-pay for eligible patients on commercial/private insurance plans* *Patients must meet certain eligibility criteria to qualify for assistance. Patients receiving reimbursement under Medicare, Medicaid, VA, DoD (TRICARE), Indian Health Services, or similar federal or state programs, may not be eligible for some assistance. Some portion of this patient assistance may be administered by Caring Voice Coalition (CVC), an independent national nonprofit organization.

• Special Populations: The use of ADCIRCA is not recommended for patients with severe renal or hepatic impairment. Please see Full Prescribing Information for dosing recommendations for patients with mild to moderate renal or hepatic impairment

• Potential Drug Interactions: ADCIRCA contains the same ingredient (tadalafil) as Cialis®, which is used to treat erectile dysfunction (ED) and the signs and symptoms of benign prostatic hyperplasia (BPH). The safety and efficacy of combinations of ADCIRCA with Cialis or other PDE-5is have not been studied. Therefore, the use of such combinations is not recommended

• Vision/Hearing: Patients who experience a sudden loss of vision in one or both eyes, which could be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), or sudden decrease or loss of hearing after taking ADCIRCA should seek immediate medical attention

• Prolonged Erection: In rare instances, men taking PDE-5is (including tadalafil) for ED reported an erection lasting more than four hours. Male patients who experience a prolonged erection should seek immediate medical attention

ADVERSE REACTIONS

• Adverse Reactions: The most common adverse event with ADCIRCA is headache (42% ADCIRCA vs 15% placebo). Other common adverse events (reported by ≥9% of patients on ADCIRCA and more frequent than placebo by 2%) include myalgia (14% vs 4%), nasopharyngitis (13% vs 7%), flushing (13% vs 2%), respiratory tract infection (13% vs 6%), extremity pain (11% vs 2%), nausea (11% vs 6%), back pain (10% vs 6%), dyspepsia (10% vs 2%), and nasal congestion (9% vs 1%)1

Please see brief summary of Full Prescribing Information on following page. Please see Full Prescribing Information and Patient Information available at www.adcirca.com, or call 1-800-545-5979. www.adcirca.com 1-877-UNITHER

ADCIRCA® (tadalafil) tablets is a phosphodiesterase 5 inhibitor (PDE-5i) indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class II–III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).
ADCIIRA® (tadalafil) tablets

BRIEF SUMMARY

The following is a brief summary of the full prescribing information on ADCIRCA (tadalafil). Please review the full prescribing information prior to prescribing ADCIRCA.

INDICATIONS AND USAGE

Pulmonary Arterial Hypertension: ADCIRCA is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominantly patients with NYHA Functional Class II–III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).

CONTRAINDICATIONS

Concomitant Organic Nitrates: Do not use ADCIRCA in patients with any form of organic nitrate, either regular or intermittently. ADCIRCA potentiates the hypotensive effect of nitrates. This potentiation is thought to result from the combined effects of nitrates and ADCIRCA on the nitric oxide/cGMP pathway.

Hypersensitivity Reactions: ADCIRCA is contraindicated in patients with a known serious hypersensitivity to tadalafil (ADCIIRA or CIALIS). Hypersensitivity reactions have been reported, including Stevens–Johnson syndrome and exfoliative dermatitis.

WARNINGS AND PRECAUTIONS

Cardiovascular Effects: Discuss with patients the appropriate action to take in the event that they experience anginal chest pain requiring nitroglycerin following intake of ADCIRCA. At least 48 hours should elapse after the last dose of ADCIRCA prior to administration of nitroglycerin. If a patient has taken ADCIRCA within 48 hours, administer nitrates under close medical supervision with appropriate hemodynamic monitoring. Patients who experience anginal chest pain after taking tadalafil should seek immediate medical attention. PDE5 inhibitors, including tadalafil, have mild systemic vasodilatory properties that may result in transient decreases in blood pressure. Prior to prescribing ADCIRCA, carefully consider whether patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects. Patients with severely impaired autonomic control of blood pressure or with left ventricular outflow obstruction (e.g., aortic stenosis and idiopathic hypertrophic subaortic stenosis) may be particularly sensitive to the actions of vasodilators, including PDE5 inhibitors. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Since there are no clinical data on administration of ADCIRCA to patients with veno-occlusive disease, administration of ADCIRCA to such patients is not recommended. Should signs of pulmonary edema occur when ADCIRCA is administered, the possibility of associated PVOD should be considered. There is a lack of data on safety and efficacy in the following groups who were specifically excluded from the PAH clinical trials:

- Patients with clinically significant aortic and mitral valve disease
- Patients with pericardial constriction
- Patients with restrictive or constrictive cardiomyopathy
- Patients with significant left ventricular dysfunction

Use with Alpha Blockers and Antihypertensives — PDE5 inhibitors, including ADCIRCA, and α-adrenergic blocking agents and antihypertensives can cause hypotension, especially when taken in combination, a additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes may lower blood pressure significantly, which may lead to symptomatic hypotension (e.g., fainting). Safety of combined use of PDE5 inhibitors and alpha blockers may be affected by other variables, including intravascular volume depletion and use of other antihypertensive drugs. Use with Alcohol — Both alcohol and tadalafil are metabolized by the liver. When both drugs are taken in combination, blood pressure-lowering effects are increased. Use with Potent CYP3A Inhibitors or Inducers: Co-administration of ADCIRCA in Patients on Ritonavir — In patients who have taken ritonavir within 48 hours, administer nitrates under close medical supervision with appropriate hemodynamic monitoring. Patients who experience anginal chest pain after taking tadalafil should seek immediate medical attention. PDE5 inhibitors, including tadalafil, are metabolized predominantly by CYP3A in the liver. In patients taking potent inhibitors of CYP3A such as ketoconazole and triple-dose ritonavir, the use of ADCIRCA potentiates the hypotensive effect of nitrates. This potentiation is thought to result from the combined effects of nitrates and ADCIRCA on the nitric oxide/cGMP pathway.

Hearing Impairment: There have been rare reports of hearing loss or decreased hearing following tadalafil administration, including cases of abrupt hearing loss. These events have been reported in patients with normal hearing at the time of tadalafil administration. The relationship of tadalafil to these events has not been established. Use with Other PDE5 Inhibitors: Tadalafil is also marketed as CIALIS. The safety and efficacy of taking CIALIS together with CILAG or other PDE5 inhibitors have not been studied. Inform patients taking ADCIRCA not to take CIALIS or other PDE5 inhibitors.

Prolonged Erection: There have been rare reports of prolonged erections (painful erections greater than 6 hours in duration) for this class of compounds. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Patients who have an erection lasting greater than 4 hours, whether painful or not, should seek medical attention. ADCIRCA should be used with caution in patients who have conditions that might predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia), or in patients with anatomic deformations of the penis (such as anulogulation, cavernosal fibrosis, or Peyronie’s disease).

Effect on Bleeding: PDE5 is found in platelets. When administered in combination with aspirin, tadalafil 20 mg did not prolong bleeding time, relative to aspirin alone. ADCIRCA has not been administered in patients with aspirin or other anticoagulants, including heparin. Use with other medications that prolong bleeding time or increase risk of bleeding should be considered.

ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in this labeling:

- Hypotension
- Visual loss
- Priapism

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates observed in another drug and may not reflect the rates observed in practice. Tadalafil was administered to 398 patients with PAH during clinical trials worldwide. In trials of ADCIRCA, a total of 311 and 251 subjects have been treated for at least 182 days and 360 days, respectively. The overall rates of discontinuation because of an adverse event (AE) in the placebo-controlled trial were 9% for ADCIRCA 40 mg and 15% for placebo. The rates of discontinuation due to AEs, other than those related to worsening of PAH, in patients treated with ADCIRCA 40 mg was 4% compared to 5% in placebo-treated patients. In the placebo-controlled study, the most common AEs were headache and myalgia. Table 1 presents treatment-emergent adverse events reported by ≥9% of patients in the ADCIRCA 40 mg group and occurring more frequently than placebo.

<table>
<thead>
<tr>
<th>EVENT</th>
<th>ADCIRCA 40 mg (%N=70)</th>
<th>Placebo (%N=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Flushing</td>
<td>23</td>
<td>10</td>
</tr>
<tr>
<td>Respiratory Tract Infection</td>
<td>24</td>
<td>13</td>
</tr>
</tbody>
</table>

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of tadalafil. These events have been chosen for inclusion either because of their seriousness, reporting frequency, lack of clear alternative causation, or if the event was not included in the clinical trials. These adverse events are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure. The list does not include adverse events that are reported from clinical trials and that are listed elsewhere in the section. Cardiovascular and cerebrovascular — Serious cardiovascular events, including myocardial infarction, sudden cardiac death, stroke, chest pain, palpitations, and tachycardia, have been reported postmarketing in temporal association with the use of tadalafil. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of tadalafil without sexual activity. Others were reported to have occurred hours to days after the use of tadalafil and sexual activity. It is not possible to determine whether these events are related directly to tadalafil, to sexual activity, to the patient’s underlying cardiovascular disease, or to a combination of these factors. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure. The list does not include adverse events that are reported from clinical trials and that are listed elsewhere in the section. Cardiovascular and cerebrovascular — Serious cardiovascular events, including myocardial infarction, sudden cardiac death, stroke, chest pain, palpitations, and tachycardia, have been reported postmarketing in temporal association with the use of PDE5 inhibitors, including tadalafil. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of tadalafil without sexual activity. Others were reported to have occurred hours to days after the use of tadalafil and sexual activity. It is not possible to determine whether these events are related directly to tadalafil, to sexual activity, to the patient’s underlying cardiovascular disease, or to a combination of these factors.

- Body as a whole — Hypersensitivity reactions including urticaria, Stevens–Johnson syndrome, and exfoliative dermatitis. Nervous — Migraine, seizure and seizure like activity, generalised convulsion. Ophthalmologic — Visual field defect, retinal vein occlusion, and retinal artery occlusion. Non–arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision, involving permanent loss of vision, has been reported rarely postmarketing in temporal association with the use of PDE5 inhibitors, including tadalafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for development of NAION, including but not necessarily limited to: low cup to disc ratio (“crowded disc”), age over 50, diabetes, hypertension, hyperlipidemia, smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient’s underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors. Obstetric — Cases of sudden decrease or loss of hearing have been reported postmarketing in temporal association with the use of PDE5 inhibitors, including tadalafil. In some of the cases, medical conditions and other factors were reported that may have played a role in the otologic adverse events. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of tadalafil, to the patient’s underlying vascular risk factors for hearing loss, a combination of these factors, or to other factors. Urogenital — Priapism.

DRUG INTERACTIONS

Potential for Pharmacodynamic Interactions with ADCIRCA: Nitrates — Do not use ADCIRCA in patients who...
are using any form of organic nitrate. Clinical pharmacology studies ADCIRCA potentiated the hypotensive effect of nitrates. In a patient who has taken ADCIRCA, where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should elapse after the last dose of ADCIRCA before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring. Alpha-Blockers — PDE5 inhibitors, including ADCIRCA, and alpha-adrenergic blocking agents are both vasodilators with blood-pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. Clinical pharmacology studies have been conducted with coadministration of tadalafil with doxazosin, alfuzosin or tamsulosin. Antihypertensives — PDE5 inhibitors, including ADCIRCA, are mild systemic vasodilators. Clinical pharmacology studies were conducted to assess the effect of tadalafil on the potentiation of the blood-pressure-lowering effects of selected antihypertensive medications (amiloride, angiotensin II receptor blockers, bendroflumethiazide, enalapril, and metoprolol). Small reductions in blood pressure occurred following coadministration of tadalafil with these agents compared with placebo. Alcohol — Both alcohol and tadalafil, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood pressure-lowering effects of each individual compound may be increased. Substance consumption of alcohol (e.g., 5 units or greater) in combination with ADCIRCA can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache. Tadalafil (10 mg or 20 mg) did not affect alcohol plasma concentrations and alcohol did not affect tadalafil plasma concentrations. Potential for Other Drugs to Affect ADCIRCA: Ritonavir — Ritonavir initially inhibits and later induces CYP3A, the enzyme involved in the metabolism of tadalafil. At steady state of ritonavir (about 1 week), the exposure to tadalafil is similar as in the absence of ritonavir. Other Potential Inhibitors of CYP3A — Tadalafil is metabolized predominantly by CYP3A in the liver. In patients taking potent inhibitors of CYP3A such as ketoconazole, and itraconazole, avoid use of ADCIRCA. Potential Inducers of CYP3A — For patients chronically taking potent inducers of CYP3A, such as rifampin, avoid use of ADCIRCA. Potential for ADCIRCA to Affect Other Drugs: Cytochrome P450 Substrates — Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolized by cytochrome P450 (CYP) isofoms (e.g., theophylline, warfarin, midazolam, levastatin, bosentan). Aspirin — Tadalafil (10 mg and 20 mg once daily) does not potentiate the increase in bleeding time caused by aspirin. P-glycoprotein (e.g., digoxin) — Coadministration of tadalafil (40 mg once daily) for 10 days did not significantly alter digoxin pharmacokinetics in healthy subjects. USE IN SPECIFIC POPULATIONS Pregnancy: Pregnancy Category B — Animal reproduction studies in rats and mice revealed no evidence of fetal harm. There are, however, no adequate and well-controlled studies of tadalafil in pregnant women. Because animal reproduction studies are not always predictive of human response, tadalafil should be used during pregnancy only if clearly needed. Non-teratogenic effects — Animal reproduction studies showed no evidence of teratogenicity, embryotoxicity, or fetotoxicity when tadalafil was given to pregnant rats or mice at unbound tadalafil exposures up to 7 times the maximum recommended human dose (MRHD) of 40 mg/day during organogenesis. In one of two perinatal/postnatal developmental studies in rats, postnatal pup survival decreased following maternal exposure to unbound tadalafil concentrations greater than 5 times the MRHD based on AUC. Signs of maternal toxicity occurred at doses greater than 8 times the MRHD based on AUC. Surviving offspring had normal development and reproductive performance. Nursing Mothers: It is not known whether tadalafil is excreted into human milk. While tadalafil or some metabolite of tadalafil was excreted into rat milk, drug levels in animal breast milk may not accurately predict levels of drug in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when ADCIRCA is administered to a nursing woman. Pediatric Use: Safety and effectiveness of ADCIRCA in pediatric patients have not been established. Geriatric Use: Of the total number of subjects in the clinical study of tadalafil for pulmonary arterial hypertension, 28 percent were 65 and over, while 8 percent were 75 and over. No overall differences in safety were observed between subjects over 65 years of age compared to younger subjects or those over 75 years of age. No dose adjustment is warranted based on age alone; however, a greater sensitivity to medications in some older individuals should be considered. Renal Impairment: For patients with mild or moderate renal impairment, start ADCIRCA at 20 mg once daily. Increase the dose to 40 mg once daily based upon individual tolerability. In patients with severe renal impairment, avoid use of ADCIRCA because of increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis. Hepatic Impairment: Because of limited clinical experience in patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A or B), consider a starting dose of ADCIRCA 20 mg once daily. Patients with severe hepatic cirrhosis (Child-Pugh Class C) have not been studied, thus avoid use of ADCIRCA in such patients. OVERDOSAGE Single doses up to 500 mg have been given to healthy male subjects, and multiple daily doses up to 100 mg have been given to male patients with erectile dysfunction. Adverse reactions were similar to those seen at lower doses. Doses greater than 40 mg have not been studied in patients with pulmonary arterial hypertension. In cases of overdose, standard supportive measures should be adopted as needed. Hemodialysis contributes negligibly to tadalafil elimination. Marketed by: Lung LLC, a wholly-owned subsidiary of United Therapeutics Corporation Rx only www.adcirca.com BS.HCP.KGKLUNGLLC-4-72.v1

The Specialty Pharmacy Advisory Board wants to hear from you!

The Specialty Pharmacy Advisory Board involves a cross section of the pulmonary hypertension community, including patients and their loved ones, as well as specialty pharmacy representatives. A collaboration between the Pulmonary Hypertension Association and the Caring Voice Coalition, we're dedicated to gathering feedback about how well specialty pharmacies are serving PH patients and using that feedback to promote improved service.

Submit your comments at www.PHAassociation.org/SpecialtyPharmacyResponseForm or by calling 301-565-3004 x773

Pulmonary Hypertension Association
Empowered by hope
When Is Testing Beyond Overnight Oximetry Indicated for Assessment of Sleep-Disordered Breathing in Pulmonary Arterial Hypertension?

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New York, NY

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Sleep-disordered breathing (SDB) is an overarching term encompassing several medical conditions in which breathing diminishes or ceases during sleep, often resulting in daytime sleepiness and reduced quality of life. Obesity is strongly associated with SDB and both conditions are increasing in prevalence in the United States. The pathophysiology of SDB is complex, although treatment approaches including weight loss and limiting intermittent hypoxemia have received the most attention as measures to improve PH. Clinical consensus recommendations state that treatment of PH in the setting of SDB may be appropriate when PH persists despite adequate therapy for SDB. Current clinical research is also investigating the possibility that pulmonary arterial hypertension (PAH) may actually worsen or cause SDB, a reversal of the traditional paradigm that SDB produces PH. However, before a clinician may consider the ideal treatment approach for an individual patient with PH, it is imperative that SDB is either excluded or diagnosed and characterized.

Consensus statements have recommended the use of overnight oximetry as the initial pivotal test for SDB screening, with an overnight polysomnography (PSG) performed as a contingent test when necessary. Two questions that follow include: (1) When is overnight oximetry considered sufficiently abnormal to warrant further investigation? and (2) Are there circumstances when pretest probability is high enough to proceed directly to PSG? There is no universally accepted definition of oxygen desaturation in SDB. A study reviewing overnight oximetry results showed that the mean lowest oxygen saturation in 350 normal subjects was 90.4% (±3.1%) vs 65.9% (±22.6%) in 25 subjects with obstructive sleep apnea, demonstrating not only the differences between groups but also significant variability within patients with SDB. The most commonly published definition of oxygen desaturation in SDB is a decrease of ≥4% from baseline. Calculating the oxygen desaturation index (ODI), however, which is the number of desaturations per hour of sleep, may more closely correlate with the apnea-hypopnea index obtained from PSG testing. The threshold for an abnormal ODI has been studied at ≥5, ≥10, and ≥15 desaturations per hour with little evidence to suggest one of these cutoffs as the most valid. Overnight oximetry reports may not always contain detailed data that are conducive to waveform analysis and, since they are unmonitored, they are subject to repeated artifacts, which may limit accurate interpretation. While overnight oximetry is accessible and relatively inexpensive, the results are only valuable when they are interpreted correctly and may benefit from a universal definition of desaturation in relation to ODI.

Compared to oximetry as a single test measurement, the typical PSG monitors approximately a dozen parameters (of which oximetry is just one) suggesting that the PSG is better suited to characterize SDB. However, a traditional overnight sleep laboratory-based PSG is an expensive test with limited availability in many areas. An argument can be made against screening all PH patients with PSG for several reasons: it is costly, labor intensive, time consuming, and requires an overnight stay at a sleep center. Furthermore, limited access in some regions may result in long wait times and delays in treatment, which may contribute to clinical worsening in PH.

However, PH patients with a high pretest probability of SDB may benefit from a screening approach that begins with a nocturnal PSG in lieu of nocturnal oximetry. Utilizing a clinical prediction assessment for SDB can help identify those who warrant initial PSG screening. For example, Flemons and colleagues developed a clinical prediction model for SDB based on increasing neck circumference, hypertension, habitual snoring, and bed partner reports of nocturnal gasping or choking. Table 1 contains the major risk factors to consider in your clinical assessment.

Ambulatory diagnosis of SDB with home sleep testing (HST) is an increasingly attractive option that may offer an efficient compromise between the limited data obtained from overnight oximetry and the cost, time, and scheduling requirements of a laboratory-based PSG. Home sleep testing is becoming increasingly popular and is covered by most insurance plans. Recent studies com-

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paring clinical outcomes support the use of HST for patients with high pretest probability of SDB, though widespread utility is limited by inadequate standardization and paucity of data that convincingly demonstrate its cost effectiveness. In summary, the current evaluation algorithm for evaluating SDB in patients with PH recommends that patients receive initial testing with overnight oximetry and those with abnormal results undergo nocturnal PSG testing. An oximetry result demonstrating an ODI of ≥5 to ≥15 events per hour may represent a prudent cutoff for proceeding to PSG testing. However, patients with sufficient risk factors for SDB may be appropriate for proceeding directly to initial testing with PSG (Table 1). A sleep laboratory-based PSG remains the established standard; however, HST may be a sufficient alternative in some patients. Consultation with a sleep specialist to help facilitate diagnosis and treatment of SDB and monitor treatment compliance in PH patients is recommended.

References

Table 1. Risk factors for sleep apnea that increase the likelihood that a PSG will be necessary during the PH evaluation

<table>
<thead>
<tr>
<th>Risk Factor</th>
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<tbody>
<tr>
<td>Male gender</td>
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<tr>
<td>Postmenopausal state</td>
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<tr>
<td>Excess body weight (BMI &gt;30)</td>
</tr>
<tr>
<td>Increasing age (especially after age 60)</td>
</tr>
<tr>
<td>Race (risk higher with non-Caucasian races)</td>
</tr>
<tr>
<td>Craniofacial anatomy (especially higher Mallampati score, retrognathia)</td>
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<tr>
<td>Familial and genetic predisposition</td>
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</tbody>
</table>

Modified from Young et al.10

A Study to Test the Effects of Riociguat in Patients With Pulmonary Hypertension Associated With Left Ventricular Systolic Dysfunction (LEPHT)

Section Editor
Fernando Torres, MD

The Clinical Trials Update highlights new and ongoing research trials that are evaluating therapies for PAH. In this issue, Fernando Torres, MD, examines a study on patients with pulmonary hypertension associated with left ventricular systolic dysfunction.

Pulmonary hypertension (PH) associated with left heart disease has been a challenge for the PH community. Though most of us have concentrated our efforts on managing the patients who have PH with normal systolic heart function, there is another population of patients with PH with decreased left ventricular heart function who also are at risk of poor survival. It is known that patients with high mean pulmonary arterial pressure (mPAP) and left ventricular ejection fraction (LVEF) less than 45% carry a high mortality compared to those with normal mPAP. Thus, finding new therapies for this population would be advantageous.

In 2009, a single-dose study with riociguat was found to decrease the mPAP, wedge, and pulmonary vascular resistance (PVR) of patients with high mPAP and left heart failure. This then prompted the design and completion of LEPHT.

LEPHT enrolled about 200 patients worldwide. All patients had a screening right heart catheterization in which the mPAP was higher than 25 mm Hg, and all had an LVEF <45% at inclusion to the study. They were all maximally medically treated, and their heart failure medications could not have changed in the month prior, with the exception of diuretics, which could have been changed up to a week prior to randomization. The patients were randomized to placebo or riociguat of 0.5, 1, or 2 mg TID in four parallel arms. After 16 weeks, the patients had a repeat right heart catheterization and the primary endpoint of decrease in mPAP was evaluated. Secondary endpoints included other hemodynamic parameters, 6-minute walk distance (6MWD), N-terminal pro-brain natriuretic peptide (NT-proBNP) as well as quality of life questionnaire.

The results of the trial were presented recently at the American Heart Association annual meeting in Dallas and showed a decrease in the mPAP that was not statistically significant. The change in cardiac index, systemic vascular resistance, and PVR showed statistically significant improvements. Quality of life markers also were positive and the medication was tolerated well.

Though the primary endpoint was not achieved, there were some markers in the hemodynamics that were favorable. Thus, there is still hope that riociguat may have a role in the treatment of PH associated with left heart disease. A large multicenter clinical trial is now being planned to look at the efficacy and safety of using riociguat for the treatment of patients with PH and preserved LVEF (HFP EF). DILATE is another smaller study finished in Austria with 39 patients looking at the effects of riociguat for the treatment of PH with left heart diastolic dysfunction. The results of these trials are anticipated in the near future.
Now approved

Please see Brief Summary of Prescribing Information, including BOXED WARNING for embryo-fetal toxicity, on adjacent pages.
INDICATIONS AND USAGE

Pulmonary Arterial Hypertension

OPSUMIT® is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group II) to delay disease progression. Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment). OPSUMIT also reduced hospitalization for PAH.

Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years. Patients were treated with OPSUMIT monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids. Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%).

CONTRAINDICATIONS

Pregnancy

OPSUMIT may cause fetal harm when administered to a pregnant woman. OPSUMIT is contraindicated in females who are pregnant. OPSUMIT was consistently shown to cause fetal harm when administered to pregnant animals. OPSUMIT may cause fetal harm when administered during pregnancy and is contraindicated for use in females who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, ensure use of acceptable methods of contraception [see Warnings and Precautions (Embryo-Fetal Toxicity)]. OPSUMIT is available only through a restricted program called the OPSUMIT REMS Risk Evaluation and Mitigation Strategy (REMS) [see Warnings and Precautions (OPSUMIT REMS Program)].

OPSUMIT REMS Program

For all female patients, OPSUMIT is available only through a restricted program called the OPSUMIT REMS Program, a restricted distribution program [see Warnings and Precautions (OPSUMIT REMS Program)].

CONTRAINDICATIONS

Pregnancy

OPSUMIT may cause fetal harm when administered to a pregnant woman. OPSUMIT is contraindicated in females who are pregnant. OPSUMIT was consistently shown to have teratogenic effects when administered to animals. If OPSUMIT is used during pregnancy, advise the patient of the potential hazard to a fetus [see Warnings and Precautions (Embryo-Fetal Toxicity) and Use in Specific Populations (Pregnancy)].

OPSUMIT is available for females through the OPSUMIT REMS Program, a restricted distribution program [see Warnings and Precautions (OPSUMIT REMS Program)].

Hepatotoxicity

Other ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. The incidence of elevated aminotransferases in the study of OPSUMIT in PAH is shown in Table 1.

Table 1: Incidence of Elevated Aminotransferases in the SERAPHIN Study

<table>
<thead>
<tr>
<th></th>
<th>OPSUMIT 10 mg (N=242)</th>
<th>Placebo (N=249)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3 x ULN</td>
<td>3.4%</td>
<td>4.5%</td>
</tr>
<tr>
<td>&gt;5 x ULN</td>
<td>2.1%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

In the placebo-controlled study of OPSUMIT, discontinuations for hepatic adverse events were 3.3% in the OPSUMIT 10 mg group vs. 1.6% for placebo. Obtain liver enzyme tests prior to initiation of OPSUMIT and repeat during treatment as clinically indicated. Advise patients to report symptoms suggesting hepatic injury (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching). If clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2 x ULN, or by clinical symptoms of hepatotoxicity, discontinue OPSUMIT. Consider re-initiation of OPSUMIT when hepatic enzyme levels normalize in patients who have not experienced clinical symptoms of hepatotoxicity.

Decreased Hemoglobin

Decreases in hemoglobin concentration and hematocrit have occurred following administration of other ERAs and were observed in clinical studies with OPSUMIT. These decreases occurred early and stabilized thereafter. In the placebo-controlled study of OPSUMIT in PAH, OPSUMIT 10 mg caused a mean decrease in hemoglobin from baseline to up to 18 months of about 1.0 g/dL compared to no change in the placebo group. A decrease in hemoglobin to below 10.0 g/dL was reported in 8.7% of the OPSUMIT 10 mg group and in 3.4% of the placebo group. Decreases in hemoglobin seldom required treatment discontinuation. Initiation of OPSUMIT is not recommended in patients with severe anemia. Measure hemoglobin prior to initiation of treatment and repeat during treatment as clinically indicated [see Adverse Reactions (Clinical Trial Experience)].

Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)

Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue OPSUMIT.

Decreased Sperm Counts

Other ERAs have caused adverse effects on spermatogenesis. Counsel men about potential effects on fertility [see Use in Specific Populations (Females and Males of Reproductive Potential) and Nonclinical Toxicology (Carcinogenesis, Mutagenesis, Impairment of Fertility)].

ADVERSE REACTIONS

Clinically significant adverse reactions that appear in other sections of the labeling include:

- Embryo-fetal Toxicity [see Warnings and Precautions (Embryo-Fetal Toxicity)]
- Hepatotoxicity [see Warnings and Precautions (Hepatotoxicity)]
- Decrease in Hemoglobin [see Warnings and Precautions (Hemoglobin Decrease)]

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Safety data for OPSUMIT were obtained primarily from one placebo-controlled clinical study in 742 patients with PAH (SERAPHIN study). The exposure to OPSUMIT in this trial was up to 3.8 years with a median exposure of about 2 years (N=542 for 1 year; N=429 for 2 years; and N=88 for more than 3 years). The overall incidence of treatment discontinuations because of adverse events was similar across OPSUMIT 10 mg and placebo treatment groups (approximately 11%).

Table 2 presents adverse reactions more frequent on OPSUMIT than on placebo by ≥3%.

Table 2: Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>OPSUMIT 10 mg (N=242)</th>
<th>Placebo (N=249)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>13%</td>
<td>3%</td>
</tr>
<tr>
<td>Nasopharyngitis/pharyngitis</td>
<td>20%</td>
<td>13%</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>12%</td>
<td>6%</td>
</tr>
<tr>
<td>Headache</td>
<td>14%</td>
<td>9%</td>
</tr>
<tr>
<td>Influenza</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>9%</td>
<td>6%</td>
</tr>
</tbody>
</table>

DRUG INTERACTIONS

Strong CYP3A4 Inducers

Strong inducers of CYP3A4 such as rifampin significantly reduce macitentan exposure. Concomitant use of OPSUMIT with strong CYP3A4 inducers should be avoided [see Clinical Pharmacology (Pharmacokinetics)].
**Strong CYP3A4 Inhibitors**

Concomitant use of strong CYP3A4 inhibitors like ketoconazole approximately double macitentan exposure. Many HIV drugs like ritonavir are strong inhibitors of CYP3A4. Avoid concomitant use of OPSUMIT with strong CYP3A4 inhibitors [see Clinical Pharmacology (Pharmacokinetics)]. Use other PAH treatment options when strong CYP3A4 inhibitors are needed as part of HIV treatment [see Clinical Pharmacology (Pharmacokinetics)].

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Pregnancy Category X.**

**Risk Summary**

OPSUMIT may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. Macitentan was teratogenic in rabbits and rats at all doses tested. A no-effect dose was not established in either species. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential hazard to a fetus [see Contraindications (Pregnancy)].

**Animal Data**

In both rabbits and rats, there were cardiovascular and mandibular arch fusion abnormalities. Administration of macitentan to female rats from late pregnancy through lactation caused reduced pup survival and impairment of the male fertility of the offspring at all dose levels tested.

**Nursing Mothers**

It is not known whether OPSUMIT is present in human milk. Macitentan and its metabolites were present in the milk of lactating rats. Because many drugs are present in human milk and because of the potential for serious adverse reactions from macitentan in nursing infants, nursing mothers should discontinue nursing or discontinue OPSUMIT.

**Pediatric use**

The safety and efficacy of OPSUMIT in children have not been established.

**Geriatric use**

Of the total number of subjects in the clinical study of OPSUMIT for PAH, 14% were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

**Females and Males of Reproductive Potential**

**Females**

**Pregnancy Testing:** Female patients of reproductive potential must have a negative pregnancy test prior to starting treatment with OPSUMIT and monthly pregnancy tests during treatment with OPSUMIT. Advise patients to contact their health care provider if they become pregnant or suspect they may be pregnant. Perform a pregnancy test if pregnancy is suspected for any reason. For positive pregnancy tests, counsel patients on the potential risk to the fetus [see Boxed Warning and Dosage and Administration section 2.2 in full Prescribing Information].

**Contraception:** Female patients of reproductive potential must use acceptable methods of contraception during treatment with OPSUMIT and for 1 month after treatment with OPSUMIT. Patients may choose one highly effective form of contraception (intrauterine devices (IUD), contraceptive implants or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a partner’s vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider trained in contraceptive counseling [see Boxed Warning].

**Testicular effects:** Like other endothelin receptor antagonists, OPSUMIT may have an adverse effect on spermatogenesis [see Warnings and Precautions (Decreased Sperm Counts) and Nonclinical Toxicology (Carcinogenesis, Mutagenesis, Impairment of Fertility)].

**OVERDOSAGE**

OPSUMIT has been administered as a single dose of up to and including 600 mg to healthy subjects (60 times the approved dosage). Adverse reactions of headache, nausea and vomiting were observed. In the event of an overdose, standard supportive measures should be taken, as required. Dialysis is unlikely to be effective because macitentan is highly protein-bound.

**CLINICAL PHARMACOLOGY**

**Pharmacokinetics**

**Special Populations**

There are no clinically relevant effects of age, sex, or race on the pharmacokinetics of macitentan and its active metabolite.

**Renal impairment:** Exposure to macitentan and its active metabolite in patients with severe renal impairment (CrCl 15-29 mL/min) compared to healthy subjects was increased by 30% and 80%, respectively. This increase is not considered clinically relevant.

**Hepatic impairment:** Exposure to macitentan was decreased by 21%, 34%, and 6% and exposure to the active metabolite was decreased by 20%, 25%, and 25% in subjects with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, and C), respectively. This decrease is not considered clinically relevant.

**Drug Interactions**

**In vitro studies**

At plasma levels obtained with dosing at 10 mg once daily, macitentan has no relevant inhibitory or inducing effects on CYP enzymes, and is neither a substrate nor an inhibitor of the multi-drug resistance protein (P-gp, MDR-1). Macitentan and its active metabolite are neither substrates nor inhibitors of the organic anion transporting polypeptides (OATP1B1 and OATP1B3) and do not significantly interact with proteins involved in hepatic bile salt transport, i.e., the bile salt export pump (BSEP) and the sodium-dependent taurocholate-co-transporting polypeptide (NTCP).

**In vivo studies**

**Effect of other drugs on macitentan:** The effect of other drugs on macitentan and its active metabolite are studied in healthy subjects and are shown in Figure 1 below.

**Figure 1**

Interacting drug | Macitentan | Active metabolite | Recommendation
--- | --- | --- | ---
Sildenafil | No dose adjustment | No dose adjustment | Avoid
Cyclosporine A | No dose adjustment | No dose adjustment | Avoid
Ketoconazole | | | Avoid
Ritonavir | | | Avoid

Effects of other strong CYP3A4 inhibitors such as ritonavir on macitentan were not studied, but are likely to result in an increase in macitentan exposure at steady state similar to that seen with ketoconazole [see Drug Interactions (Strong CYP3A4 Inhibitors)].

**Effect of macitentan on other drugs**

**Warfarin:** Macitentan once daily dosing did not alter the exposure to R- and S-warfarin or their effect on international normalized ratio (INR).

**Sildenafil:** At steady-state, the exposure to sildenafil 20 mg t.i.d. increased by 15% during concomitant administration of macitentan 10 mg once daily. This change is not considered clinically relevant.

**NONCLINICAL TOXICOLOGY**

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

**Carcinogenesis:** Carcinogenicity studies of 2 years’ duration did not reveal any carcinogenic potential at exposures 75-fold and 140-fold the human exposure (based on AUC) in male and female mice, respectively, and 8.3- and 42-fold in male and female rats, respectively.

**Mutagenesis:** Macitentan was not genotoxic in a standard battery of in vitro and in vivo assays that included a bacterial reverse mutation assay, an assay for gene mutations in mouse lymphoma cells, a chromosome aberration test in human lymphocytes, and an in vivo micronucleus test in rats.

**Impairment of Fertility:** Treatment of juvenile rats from postnatal Day 4 to Day 114 led to reduced body weight gain and testicular tubular atrophy at exposures 7-fold the human exposure. Fertility was not affected. Reversible testicular tubular dilatation was observed in chronic toxicity studies at exposures greater than 7-fold and 23-fold the human exposure in rats and dogs, respectively. After 2 years of treatment, tubular atrophy was seen in rats at 4-fold the human exposure. Macitentan did not affect male or female fertility at exposures ranging from 19- to 44-fold the human exposure, respectively, and had no effect on sperm count, motility, and morphology in male rats. No testicular findings were noted in mice after treatment up to 2 years.

**Animal Toxicology**

In dogs, macitentan decreased blood pressure at exposures similar to the therapeutic human exposure. Intimal thickening of coronary arteries was observed at 17-fold the human exposure after 4 to 39 weeks of treatment. Due to the species-specific sensitivity and the safety margin, this finding is considered not relevant for humans. There were no adverse liver findings in long-term studies conducted in mice, rats, and dogs at exposures of 12- to 116-fold the human exposure.

**Manufactured for:**

Actelion Pharmaceuticals US, Inc.
5000 Shoreline Court, Ste. 200
South San Francisco, CA 94080, USA
AC720131018

**Reference:** 1. OPSUMIT full Prescribing Information. Actelion Pharmaceuticals US, Inc. October 2013

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Pulmonary Hypertension and Chronic Obstructive Pulmonary Disease: When Is It Out of Proportion?

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Patients with chronic obstructive pulmonary disease (COPD) often present with mild pulmonary hypertension (PH). This finding has been attributed to hypoxic pulmonary vasoconstriction. However, a small proportion of COPD patients will present with moderate or severe elevations in their pulmonary artery pressure (PAP), and these patients appear to have worsened symptoms and survival when compared to patients with milder elevations in PAP. The diagnosis of PH in COPD may be difficult, due to inaccuracies in the echocardiographic estimates of PAP in these patients. Additionally, many patients with COPD will also have comorbid conditions such as diastolic heart failure, systolic heart failure, or obstructive sleep apnea, which may cause increased pulmonary pressures through other mechanisms. Clinical trials investigating the effect of PH-specific therapy for patients with PH and COPD have been small, with mixed results. A careful evaluation for other causes of PH and hemodynamic evaluation will help guide medical therapy for this group of patients.

The diagnostic evaluation of a new patient with suspected pulmonary hypertension (PH) must be done methodically to ensure the correct diagnosis and treatment plan is assigned. An essential part of the evaluation of a patient with suspected PH is to correctly categorize their disease in the World Health Organization (WHO) classification system for PH. This system groups patients together on the basis of the underlying physiology of their pulmonary pressure elevation and possible response to therapy. Over the past 20 years, the characterization of patients with Group 1 pulmonary arterial hypertension (PAH) and development of therapy for those patients has progressed substantially. This allows for an increasingly data-driven approach to the treatment plan for these patients. However, the characterization of some of the other types of PH has not progressed as quickly. This leaves providers reaching for guidelines on the management of these patients who are also presenting with significant symptoms and morbidity. One of these more poorly characterized groups of patients is WHO Group 3: PH related to respiratory disease/hypoxia. In this article, we will review the current characterization of and data regarding a subgroup of these patients—those with chronic obstructive pulmonary disease (COPD) and PH.

PREVALENCE AND EPIDEMIOLOGY OF PH IN COPD

The prevalence of COPD in the US adult population is 6%, and it is estimated that at least 15 million Americans have a COPD diagnosis. The true prevalence of PH in the COPD population is unknown, because it is difficult to diagnose. Echocardiography is unreliable in the COPD population, leaving one without a noninvasive way to accurately obtain this information in population-based studies. However, information does exist regarding the prevalence of PH in patients with severe COPD who underwent right heart catheterization (RHC) as part of the evaluation for either lung volume reduction surgery or lung transplantation. Vizza et al described the hemodynamics of 156 patients referred for lung transplantation in the early 1990s. The mean pulmonary artery pressure (mPAP) of these patients was 25.6 mm Hg, consistent with mild PH. Fifty-nine percent of these patients also had significant right ventricular dysfunction with a right ventricular ejection fraction <45%. Scharf et al reported RHC results in patients screened for the National Emphysema Treatment Trial (NETT). Of 120 patients who underwent RHC, 91% had mild PH with mPAP >20 mm Hg. However, only 5% had severe PH (mPAP >35). Thabut et al reported a retrospective review of 215 patients who underwent RHC and were referred for lung volume reduction surgery or lung transplantation. These patients had severe COPD, with a mean FEV₁ of 23.9% of the predicted value. Most patients had mild PH with mPAP of 26.9 mm Hg (Figure 1). Pulmonary hypertension as defined by the traditional definition (mPAP >25 mm Hg) was present in 50.2% of the cohort. Severe PH (mPAP >45 mm Hg) was a

Figure 1: Pulmonary Artery Pressures in COPD Patients. Pulmonary artery pressures of patients with severe COPD, referred for lung volume reduction surgery or lung transplantation. Thabut et al. Chest. 2005;127(5):1531-1536.
rare event, occurring in only 3.7% of patients. Further, a subgroup of patients (7.4%) was identified by cluster analysis, with less impairment of their pulmonary function (FEV₁ 48.5% predicted) but severe PH (average mPAP 39.8 mm Hg). It was postulated that this subgroup of patients may have PH out of proportion to their COPD and may benefit from pulmonary vasodilator therapy. Lastly, Cuttica et al retrospectively reviewed RHC findings in 4930 COPD patients listed for lung transplantation between 1997 and 2006. In this group, 48% had mPAP ≥25 while 30% had both mPAP ≥25 and pulmonary artery occlusion pressure ≤15. Less than 1% of patients had mPAP >35. All of these patients were selected from a population referred for intervention (lung volume reduction or lung transplantation); therefore, an inherent selection bias exists. In 2005, Chaouat reported a retrospective review of 998 patients referred to their department for chronic respiratory failure management (not a surgery) and who underwent RHC as part of the evaluation. Only 27 patients had severe PH with mPAP >40 mm Hg. Of those 27, 16 had another identifiable risk factor for PH, while 11 had only COPD as an identifiable risk factor.

Thus, in COPD patients with chronic respiratory failure or those referred for surgery mild PH is fairly common, but severe PH remains rare.

Pathophysiology
The pathophysiology of PH in patients with COPD is complex and likely involves the combination of hypoxic pulmonary vasoconstriction, vascular inflammation, and loss of alveolar capillary units. Hypoxic pulmonary vasoconstriction (discussed in detail in another article in this issue) is a well-described phenomenon that preserves ventilation/perfusion matching by constricting pulmonary blood vessels in areas of lung with localized hypoxia, therefore sending blood to healthier areas of lung. However, when local hypoxia becomes more widespread, this process can produce a sustained elevation in pulmonary vascular resistance. When this process becomes chronic, pulmonary vascular remodeling ensues. Autopsy specimens from COPD patients reveal muscularization of the small pulmonary arteries, proliferation of the medial and intimal layers, and inflammatory cells in the vascular wall. Additionally, a reduction in the total number of pulmonary vessels in patients with COPD has been noted on both pathology specimens and angiographic studies.

Clinical Course
In most patients with COPD, the degree of PH is mild and its progression is slow. The natural history of this population was described by Weitzenblum and colleagues in 1979. They reported the hemodynamics of 84 patients with COPD and arterial hypoxemia. Patients underwent 2 RHCs at least 3 years apart, each measure taken at a time of disease stability. Hemodynamic measurement revealed that 34 of 84 patients had mPAP greater than 20 mm Hg at baseline, and at follow-up their mPAP had increased about 0.5 to 0.6 mm Hg. Only 28 of 84 patients increased their mPAP by 5 mm Hg or more, and those who did also exhibited more hypoxemia and hypercarbia than patients with more stable hemodynamics.

Conversely, as described in the epidemiology section, a small percentage of patients with COPD exhibit moderate to severe PH at baseline. These patients do not have the same disease stability as those patients with mild baseline disease. Oswald-Mammosser and colleagues examined a cohort of 82 patients with COPD requiring oxygen therapy and sought to describe prognostic indicators for this group. On final analysis, the 5-year survival of COPD patients with a baseline mPAP of 25 mm Hg or less was 62.2%, vs 36.6% for those patients with PH (Figure 2). Multivariate analysis revealed that PAP was a better prognostic indicator than FEV₁, or the degree of hypoxemia or hypercapnea. In the previously referenced 2005 study by Chaouat et al, the 27 out of 998 (2.7%) COPD patients with severe PH (mPAP >40) had a significantly reduced survival when compared to the rest of the COPD cohort. Therefore, while the presence of more severe PH is rare in patients with COPD, it is associated with increased mortality.

PITFALLS IN THE DIAGNOSIS OF PH IN COPD PATIENTS
Because of the prognostic significance of PH in COPD patients, it seems clinically important to identify its presence; however, making the diagnosis can be a difficult endeavor. Echocardiography, the most common screening tool for PH in the general population, is less accurate in those with COPD. Arcasoy and colleagues compared the accuracy of echocardiographic estimates of PAP to RHC measurements in 374 lung transplant candidates, the majority of which had obstructive lung disease. Fifty-two percent of pressure estimates were inaccurate (varied by more than 10 mm Hg) and 48% of patients were misclassified as having PH by echocardiography when they did not. The sensitivity and specificity of echocardiography for the presence of PH in this population were 85% and 55%, respectively (Figure 3).

Therefore, if PH is suspected, RHC is required for confirmation and correct classification of the diagnosis. But, the RHC itself also contains diagnostic pitfalls in the COPD population. Patients with pulmonary parenchymal disease may exhibit significant negative swings in pleural pressure with inspiration, which may increase both the PAP and the left ventricular afterload. Therefore, in these patients in particular, it is important that all measurements be taken at end expiration. Even at end expiration, hyperinflation with alveolar distension and increased intrathoracic...
Further, patients with overlap hypoxemia than those with SAHS and COPD exhibit more significant and these treated patients had no greater therapy, however, ameliorated this risk and the overall registry population. When compared to patients without comorbid conditions, COPD patients had a greater incidence likelihood of New York Heart Association functional class III or IV (odds ratio 2.19, P<0.001), lower 6-minute walk distance (304.5 vs 400 m), and lower 3-year survival (64.7% vs 77.4%, P<0.001).26

TREATMENT
As the previously mentioned studies demonstrate, mild PH (mPAP <30) is relatively common in the COPD population and is thought to be related to hypoxic pulmonary vasoconstriction. Therefore, the mainstays of treatment for these patients remain long-term oxygen therapy, smoking cessation, inhaled bronchodilators, and inhaled corticosteroids. However, the debate about treatment of PH in COPD surrounds those patients with mPAP >35, or the so-called “PH out of proportion to COPD” patients. The argument for treatment centers on their increased symptomatology and poorer outcomes compared with patients with COPD and milder increases in pulmonary pressures. Data are confined to a few small trials and case reports, and no large trial has specifically enrolled this “out-of-proportion” group. Thus, the debate on treatment continues.

The phosphodiesterase type 5 inhibitor sildenafil has been investigated for this group of patients in a couple of small trials. Acutely, sildenafil caused hemodynamic improvements over 1 hour in patients with COPD and PH, but this improvement was accompanied by worsened hypoxemia. This hypoxemia is likely due to obliteration of hypoxic pulmonary vasoconstriction in more
improvement on ERA therapy.29,30 Small trials of outpatient use of sildenafil were performed in a small, placebo-controlled trial in subjects with COPD and PH. There was no improvement in exercise capacity or pulmonary pressures, and oxygenation and quality of life scores decreased on therapy.31 Other small trials and case reports have shown improvement on ERA therapy.32 A larger trial is needed to definitively elucidate the role of ERA therapy in patients with COPD and PH.

Inhaled prostacyclins are a theoretically attractive option for this group of patients, because the inhaled drug will likely be preferentially delivered to better-ventilated areas of lung, perhaps offering a less deleterious effect on ventilation perfusion matching. Inhaled iloprost was investigated in patients with COPD and PH. Treatment acutely improved gas exchange and walk distance.33

Treatment trials with other agents, such as tadalafil, sildenafil, udenafil, riociguat, inhaled nitric oxide, inhaled treprostinil, and inhaled iloprost, are ongoing. As these results become available, the effect of PH-specific therapy on COPD patients should become clearer. In the interim, the decision of when to consider therapy may hinge on the clinical assessment of whether or not COPD represents the cause of PH as opposed to a comorbidity seen in association with treatable WHO Group 1 PAH. In the absence of established guidelines, this requires consideration of COPD vs PH severity as well as assessment for other associated comorbidities.

CONCLUSION
Mild PH is relatively common in patients with COPD. However, a small subgroup of patients may present with COPD and moderate-severe elevations in their PAP. Whether the pathophysiology involved in this severe PH is different from those with milder PH is unclear. In this setting, a diligent search for other contributing conditions should be undertaken. Given the high prevalence of COPD, some patients will have more than one condition contributing to PH, and those with mild COPD and more severe PH might still be categorized into WHO Group 1. Patients with severe PH and COPD have increased morbidity and mortality when compared with the milder patients. This observation spurs clinicians to consider PH treatment for patients with COPD and PH. Currently, data confirming both the safety and efficacy of PH therapy for such patients is lacking and it is hoped that future studies will lead to identification of new, effective treatments as well as subgroups of patients with COPD-associated PH more likely to respond to therapy.

References


Pulmonary Hypertension in Idiopathic Pulmonary Fibrosis

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Idiopathic pulmonary fibrosis (IPF) is a fatal lung disease with a variable natural history. Pulmonary hypertension (PH) is frequently found in patients with IPF and is associated with an almost 3-fold increase in the risk of death. Pulmonary hypoxic vasoconstriction plays an important role in the pathogenesis of PH in IPF (PH-IPF), although it has become clear that it is not the only mechanism involved. While invasive right heart catheterization is the gold standard modality of hemodynamic assessment, there has been increasing interest in noninvasive testing, such as Doppler echocardiogram, as complementary methods of assessing right ventricular function in these patients. While the expanding array of pharmacologic options for the treatment of pulmonary arterial hypertension has engendered increased interest in the application of these therapies for PH-IPF, supportive evidence for benefit is lacking.

DEFINITION AND EPIDEMIOLOGY

The Fifth Symposium on PH held in 2013 in Nice, France, classifies PH associated with IPF in “Group 3: Pulmonary hypertension due to lung disease and/or hypoxemia,” differentiating this from other etiologies of PH. PH is defined as resting mean pulmonary arterial pressure (mPAP) of ≥25 mm Hg as assessed by right heart catheterization (RHC). PH should be differentiated from pulmonary arterial hypertension (PAH), hemodynamically defined as mPAP of ≥25 mm Hg in the presence of a normal pulmonary capillary wedge pressure (PCWP) on resting RHC. It has not been established which hemodynamic definition is suitable for patients with PH-IPF. In a series of 70 patients with IPF, a receiver operating curve (ROC) analysis suggested mPAP cutoff of 17 was the best predictor for mortality, however, this has not been validated in another cohort.

There have been several publications on the incidence of PH-IPF, reporting ranges from 20% to 42% (Table 1). Several factors account for this wide incidence range. The first factor is the lack of a standardized definition for PH-IPF. Some studies used the criteria for PH and others the PAH definition. The second factor is the diagnostic method used for the PH diagnosis. While most studies used hemodynamic measurement as assessed by RHC, some included patients with PH defined by pulmonary artery systolic pressure (PASP) on echocardiograms. Finally, most studies were performed in patients being worked up for lung transplantation, since these patients routinely undergo RHC as part of their transplant evaluation. Although lung transplant is the only treatment available for IPF, the selected subgroup that receives evaluation may not be representative of the overall IPF population. Using cohorts that consist of a younger IPF population with fewer comorbidities might underestimate the “true” incidence of PH-IPF. Furthermore, the timing of evaluation for PH-IPF may affect the prevalence. It has been shown that at an earlier IPF stage hemodynamics might be normal or just mildly abnormal. Use of data from patients with more advanced disease undergoing transplant evaluation may overestimate the incidence of PH-IPF, and even in the setting of advanced disease PH progression is ongoing. A study of IPF patients awaiting lung transplantation using serial RHC data showed progressive development of PH from time of initial transplant evaluation (38.6%) to time of transplant (86.4%).

When PH is present in patients with IPF, it is generally mild to moderate. In a retrospective study of 135 patients with IPF, those with PH-IPF (defined by mPAP ≥25 mm Hg and PCWP <15 mm Hg) had mPAP of 31±6 mm Hg and mean pulmonary vascular resistance (PVR) of 5±2 Wood units. Fourteen patients (11%) had moderate to severe right ventricular (RV) dysfunction on echocardiogram. However, a minority of patients with advanced lung disease have severe PH, in which the PAP is higher than expected, and those are sometimes referred to as “out of pro-

Key Words—pulmonary fibrosis, idiopathic pulmonary fibrosis, pulmonary hypertension, pulmonary vascular disease, interstitial lung disease

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portion” PH. A definition for “out of proportion” PH has not yet been established or included in the diagnostic criteria for Group 3 PH.

**PATHOGENESIS**

The histopathologic hallmark of IPF includes heterogeneous areas of fibrosis with architectural distortion. The fibrotic zones are composed mainly of dense collagen, with scattered subepithelial foci of proliferating fibroblasts and myofibroblasts (fibroblast foci). Progressive parenchymal fibrosis then leads to pulmonary vascular destruction, the initial pathologic mechanism of PH-IPF (Figure 1, top left, A, and top right, B). Vessel ablation in areas of dense fibrosis contributes to reduction of capillary density, impaired gas exchange, and elevated PVR. However, occlusive venopathy and vascular remodeling have been found in nonfibrotic lung areas, suggesting mechanisms other than extension of fibrosis and vascular obliteration contribute to the development of PH-IPF (Figure 1, bottom left, C, and bottom right, D).

Chronic alveolar hypoxia leads to subsequent pulmonary vascular remodeling and pulmonary artery (PA) vasoconstriction, also playing a major role in the development of PH-IPF. Vessels show intimal proliferation and medial thickening of muscular pulmonary arteries and pulmonary veins. This leads to neovascularization and a redistribution of microvessels within the pulmonary interstitium. New vessels differ morphologically from normal arteries and arterioles by lacking an elastin layer, which reduces vascular compliance. Further vascular remodeling is due to overexpression of inflammatory mediators (cytokines and growth factors). In general, leukotrienes promote fibrosis, whereas prostaglandin E2 (PGE2) opposes fibrogenic responses. There is an imbalance of these factors in IPF, which favors the production of 5-lipoxygenase (a profibrotic leukotriene), and upregulation of tumor necrosis factor (TNF)-α, platelet-derived growth factor (PDGF), and fibroblast growth factor, all of which mediate lung fibrosis and vascular remodeling. There is also evidence of decreased levels of PGE2 in bronchoalveolar lavage in patients with IPF. Decreased levels of PGE2 may increase expression of TNF-α and transforming growth factor (TGF)-β, responsible for collagen deposition. Finally, genetic overexpression of the vasoconstrictor endothelin-1 (ET-1) causes pulmonary fibrosis in mice. ET-1 is highly expressed in lung tissue, bronchoalveolar lavage fluid, and serum from patients with IPF and concomitant PH. This evidence provided the rationale for performing clinical trials using prostacyclin.

<table>
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Adapted from Nathan, 2009.⁵⁵

Figure 1. Pulmonary Artery in 2 Patients With Pulmonary Hypertension in Idiopathic Pulmonary Fibrosis. Top left, A (hematoxylin-eosin, original × 25): Pulmonary artery branch (with adjacent airway) is seen in an area of dense fibrosis. Top right, B (original × 100): Higher magnification of this vessel shows medial thickening and significant intimal proliferation. Bottom left, C (original × 25): A pulmonary artery/arteriole with adjacent small airway in a lobule of relatively nonfibrotic lung tissue. Bottom right, D (original × 100): Higher magnification of this vessel shows marked medial thickening. Adapted from Patel, et al. 2007.⁸
and endothelin receptor antagonists in patients with IPF-PH.

Comorbidities, both pulmonary and nonpulmonary, frequently exist in IPF (Figure 2). These comorbidities, such as coronary artery disease, systolic or diastolic left ventricular dysfunction, obstructive sleep apnea, and recurrent venous thromboembolic events may contribute to the development of PH in patients with IPF.20 When present, they may contribute to increased mortality and should be addressed therapeutically as indicated.

DIAGNOSIS

PH-IPF symptoms are nonspecific and overlap with symptoms of IPF, making the diagnosis extremely challenging. These include resting or exertional shortness of breath, fatigue, weakness, palpitations, chest discomfort, and lightheadedness or syncope. Cardiac examination may reveal an accentuated or loud P2 component of the second heart sound, a fixed split of the second heart sound (consistent with pulmonic insufficiency), and a holosystolic tricuspid regurgitation murmur. Other physical examination signs may include RV heave, jugular venous distention, and pedal edema. These findings represent progressive RV dilation and hypertrophy leading to increased right atrial pressure, and are consistent with a more advanced disease stage.

Clinical suspicion for PH-IPF should be high in the setting of progressive exercise limitation despite stable pulmonary function testing and/or parenchymal fibrosis on a chest computed tomography (CT) scan. Once other etiologies have been ruled out (such as pulmonary embolism), these symptoms should alert a physician to possible presence of PH-IPF and may justify pursuing further diagnostic testing.

Imaging

Chest radiography (CXR) may reveal cardiomegaly and enlargement of the pulmonary arteries. Although these findings might indicate presence of PH, they are nonspecific, and normal radiographic findings do not rule out PH.13 Chest CT findings suggestive of PH include enlargement of the pulmonary trunk (PA diameter ≥29 mm), RV dilation, and ratio of the main PA to ascending aorta diameter (ratio ≥1).21 However, a study of 65 patients with IPF failed to demonstrate a correlation between mPAP on RHC and main PA diameter or fibrosis score on CT scan.22

Pulmonary Function Testing

Pulmonary function test (PFT) values are fundamental in establishing the diagnosis and severity of IPF. A restrictive pattern is typically seen in PFTs of IPF patients. There is no significant difference in the forced vital capacity (FVC) and total lung capacity (TLC) of IPF patients with and without PH.2,23 However, percentage of predicted lung diffusion capacity for carbon monoxide (DLCO %) is significantly lower in those with PH-IPF (31±10% vs 38±11%, P=0.04).2 A DLCO <30% has been shown to be associated with a 2-fold higher prevalence of PH-IPF.23 Similarly, a FVC %/DLCO % ratio >1.5 was associated with an almost 2-fold increased risk of PH-IPF.23 The combination of DLCO <40% together with the need for supplemental oxygen predicted presence of PH-IPF with a sensitivity and specificity of 65% and 94.1%, respectively.7 However, none of these associations has been sufficiently robust to serve as a diagnostic predictor of PH-IPF.

Exercise Capacity

Performance on a 6-minute walk test (6MWT) is a key component in the evaluation of IPF. Mean distance walked (144±66 vs 366±82 m; P<0.001) and the pulse oximetry saturation (SpO2) nadir (80±4% vs 88±4%; P<0.001) during the 6MWT was found to be significantly lower in PH-IPF in a recent study of patients with advanced IPF.7 Exercise desaturation to <85% had a sensitivity and specificity of 100% and 61.9%, respectively, for associated PH.24 Also, failure of the heart rate to fall 1 minute after a 6MWT was found to predict presence of PH in patients with IPF (OR 4.0, 95% 1.17-13.69, P=0.02).25

The impact of PH on gas exchange and exercise capacity was evaluated in a study of patients with pulmonary fibrosis undergoing cardiopulmonary exercise testing.26 Patients with PH showed a significantly impaired exercise tolerance, worsened ventilatory efficiency, and increased dyspnea.

Biomarkers

Circulating levels of B-type natriuretic peptide (BNP) have been used as a prognostic biomarker for PAH.27 It has been shown that plasma BNP levels are higher in patients with fibrotic lung.

Figure 2. Pathophysiology of Pulmonary Hypertension in Idiopathic Pulmonary Fibrosis. Adapted from King and Nathan, 2013.20
disease and mPAP >35 mm Hg. Elevated BNP concentrations identified significant PH with a sensitivity of 85% and specificity of 88%. However, the usefulness of BNP as a diagnostic tool is limited since elevated BNP is also present in other cardiovascular disorders such as left ventricular failure, and a normal value does not exclude PH.13,29

Echocardiogram
Doppler echocardiogram (DE) is a useful, noninvasive method of assessing RV function and PH. Indications for echocardiography to evaluate patients with chronic lung diseases include: confirmation or exclusion of PH, clarification of concomitant left heart disease, and the selection of patients for RHC necessary for the conclusive diagnosis of PH.13

There has been substantial reliance on echocardiographic estimation of PASP for the evaluation of PH. PASP calculation depends on the measurement of the peak velocity of the tricuspid regurgitation jet \( (V_{max}) \). The modified Bernoulli equation is applied to calculate the given pressure \( (P_{ASPA}) \): PASP = \( 4V_{max}^2 + P_{RAP} \), where \( P_{RAP} \) = right atrial pressure estimation determined by the variation in the size of the inferior vena cava during inspiration. In a study of patients with advanced lung disease, PASP assessed by DE had a modest correlation compared with RHC measurement \((r=0.69, P<0.0001)\). However, in those with interstitial lung disease (ILD), estimation of PASP by DE was only possible in 54% of the patients, and when obtained, it was inaccurate in 37% of cases, with a discordance of greater than 10 mm Hg. Results were similar in a group of patients with IPF, showing that measurement of PASP was possible in 54.5% of the DE, with 40% accuracy between estimated PASP by DE and measured PASP by RHC.24

Another echocardiographic measurement used in the evaluation of PAH is the tricuspid annular plane systolic excursion (TAPSE). TAPSE is the longitudinal systolic displacement of the RV base toward the RV apex and has been shown to correlate strongly with RV ejection fraction. In normal subjects, the mean TAPSE varies between 2.3 and 2.6 cm, with a TAPSE of 2.0 cm likely representing the lowest acceptable normal value. In PAH, a TAPSE <1.8 cm was associated with greater RV dysfunction, lower cardiac index, and higher mortality. In 134 patients with IPF, the mean TAPSE was 2.1 cm with a significantly lower TAPSE (1.8 cm vs 2.1 cm; \( P=0.01 \)) in those with moderate to severe RV dysfunction. TAPSE was associated with stroke volume and inversely associated with PVR, independent of age, sex, race, height, weight, and FVC.12

Dilation of the RV in presence of normal size left ventricle (LV) strongly suggests increased RV afterload. Direct measurement of the RV-to-LV diameter ratio (RV:LV) assesses the relationship between the RV and the LV, and has been used to indicate presence of PH. In IPF patients, the mean RV:LV diameter ratio was 0.9±0.3 and a ratio \( \geq 1 \) was significantly correlated with increased PVR, independent of age, sex, race, height, weight, and FVC. Therefore, echocardiographic measures of RV structure and function, particularly presence of RV dilation, RV dysfunction, and RV:LV diameter ratio >1, may suggest presence of PH-IPF and strong consideration should be given to pursue RHC.

Right Heart Catheterization
RHC is the gold standard modality for hemodynamic assessment of PH-IPF. It will confirm the diagnosis and establish its severity. At this time, RHC is not routinely recommended in patients with IPF. Current indications for RHC in chronic lung disease include: proper diagnosis of PH in candidates for transplantation; suspected “out of proportion” PH, potentially amenable to be enrolled in randomized controlled clinical trials with PAH drug therapy; frequent episodes of RV failure; and inconclusive echocardiographic study in cases with a high level of suspicion. RHC can also demonstrate presence of diastolic dysfunction, which can frequently cause PH and imparts different implications in management (aggressive diuresis, blood pressure control, etc). Moreover, RHC can provide important prognostic information that can be used in patient counseling and possibly other therapeutic considerations for a disease with no current available treatment.

CLINICAL IMPLICATIONS
IPF has a median survival of 2.5 to 5 years. Presence of PH-IPF is a poor prognostic factor and is associated with a 3-fold increased risk of death, independent of age, race, FVC percentage, 6-minute walk distance (6MWD), and other covariates, (HR 3.6; 95% CI 1.8-7.1; \( P=0.0004 \)). In one study, PH was present in 52.4% of IPF nonsurvivors compared to only 24.1% of survivors \((P=0.008)\). The 1-year mortality rate of IPF patients with PH was 28% compared to 5.5% in those without PH \((P=0.002)\) (Figure 3).

In one study, DLCO <40% predicted mortality in IPF patients (RR 2.70; 95%
CI 1.46-4.99).10 However, in another study, while FVC and DLCO were lower in nonsurvivors, they did not independently predict outcomes,7 suggesting that rapid clinical deterioration with right heart failure may occur unrelated to progression of underlying parenchymal process. In IPF, 6MWD was a better predictor of mortality than FVC,35 and a 6MWD <207 m was associated with a greater than 4-fold mortality rate (RR 4.7; 95% CI 2.5-8.9; P<0.0001).35 Similarly, heart rate recovery after 6MWT was found to predict survival in patients with IPF without PH.36 In addition, BNP has also been identified as a risk factor for death independent of lung functional impairment or hypoxemia in IPF patients.29

We have shown that increasing RV:LV diameter ratio, moderate to severe right atrial and RV dilation and moderate to severe RV dysfunction detected by DE were associated with an increased risk of death, independent of covariates (including age, sex, race, height, weight, and FVC) in patients with IPF being evaluated for lung transplantation (Table 2).12 Moreover, RV:LV diameter ratio and RV dysfunction predicted adverse outcomes independently of the presence of PH-IPF or the level of the PVR.12 The presence of an increased RV:LV diameter ratio might represent an early anatomical change in response to higher PVR prior to the development of frank RV failure, and could directly contribute to adverse outcome. This suggests that right sided heart structure and function may provide complementary information in identifying a population of patients with IPF who are at increased risk of death.12

Focusing on hemodynamics, Lettieri et al7 showed a linear correlation between mPAP and outcomes, with higher pressures associated with a greater risk of mortality (HR 1.09; CI 1.02-1.16). In our study, higher mPAP was also possibly associated with reduced survival but did not reach statistical significance.12 Higher PVR was associated with 30% increased risk for overall mortality (HR per 1 Wood unit increase 1.3; 95% CI 1.1-1.5; P=0.001).12 Right atrial pressure, cardiac output, and stroke volume were not associated with the risk of death (Table 2).12 Preoperative mPAP >35 mm Hg has also been associated with increased mortality at 3 months after lung transplantation.37

**MANAGEMENT**

There are limited data on the treatment of PH-IPF. Oxygen therapy for correction of hypoxemia decreases mortality in chronic obstructive pulmonary disease,38 but such findings have not been demonstrated or systematically evaluated in IPF.39 However, given that hypoxic vasoconstriction plays an important role in the pathogenesis of PH-IPF, the use of oxygen to maintain resting and exertional arterial oxygen saturation above 90% is recommended.

There is a growing interest in the potential benefit of PAH-specific therapies in PH-IPF (Table 3). Olschewski et al40 investigated the acute effects of inhaled nitric oxide (iNO), inhaled and intravenous prostacyclin (epoprostenol and iloprost, respectively), and calcium channel blockers (CCB) in a pilot, open-label study of patients with pulmonary fibrosis of various causes with associated PH (1 had IPF). All 4 drugs decreased mPAP and PVR; epoprostenol worsened oxygenation by increasing the ventilation/perfusion (V/Q) mismatch; and epoprostenol and CCB caused hypotension. Similarly, Ghofrani et al41 examined the acute effects of a single dose of iNO, epoprostenol, or sildenafil in 16 patients with PH associated with pulmonary fibrosis (7 with IPF). All 4 drugs decreased mPAP and PVR; epoprostenol worsened oxygenation by increasing the ventilation/perfusion (V/Q) mismatch; and epoprostenol and CCB caused hypotension. 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in the 6MWD or oxygenation with 12 weeks of inhaled iloprost.  

Endothelin receptor blockers have also been studied in IPF. Bosentan Use in Interstitial Lung Disease-1 (BUILD-1), a double-blind placebo-controlled trial, investigated the use of bosentan in 158 IPF patients. No significant improvement in 6MWD was observed after 12 months; however, there was a trend toward delaying time to death or disease progression with therapy. Subsequently, BUILD-3 evaluated 616 patients with mild, biopsy-proven IPF, but did not show delay in time to death or disease progression. Most recently, ARTEMIS-IPF examined the use of ambrisentan in IPF. This study was terminated early for futility, as ambrisentan was not effective in treating IPF and may have been associated with an increased risk of disease progression and respiratory hospitalizations. It is important to note that these 3 studies were not designed to study patients with PH-IPF, as their inclusion criteria were based on presence of IPF. A subset of 21 patients with PH associated with ILD in ARIES-3 demonstrated no improvement in 6MWD.

Collard et al performed an open-label study of 14 patients with PH-IPF, and demonstrated a significant improvement in 6MWD after 3 months of the phosphodiesterase inhibitor sildenafil. The Sildenafil Trial of Exercise Performance in IPF (STEP-IPF), a placebo-controlled trial of sildenafil in 180 patients with IPF without hemodynamically diagnosed PH, failed to meet its primary endpoint of a greater than 20% improvement in 6MWD at 12 and 24 weeks. It did show improvement in dyspnea and quality of life. Interestingly, a recent post-hoc analysis of STEP-IPF showed that the subgroup of patients with echocardiographic evidence of RV dysfunction had better preservation of exercise capacity, while subjects without RV dysfunction did not respond to therapy. This might indicate that subjects with RV dysfunction have a greater degree of circulatory limitation to exercise, and are thus apt to functionally improve in response to RV afterload reducing treatment. To determine the effect of PAH therapies on patients with PH-IPF, future studies of PH therapy may need to be focused on IPF subgroups with the combination of significantly elevated PVR and RV dysfunction, as these subjects may have greater capacity to improve.

Riociguat is the first member of a new class of vasodilating agents known as soluble guanylate cyclase stimulators that

<table>
<thead>
<tr>
<th>Author/ Journal/ Year</th>
<th>Drug</th>
<th>Group</th>
<th>PH Definition</th>
<th>N</th>
<th>Study Type</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olschewski,40 AJRCCM 1999</td>
<td>iNO, IV epoprostenol, inhaled iloprost, CCB</td>
<td>Pulm fibrosis</td>
<td>PASP &gt;50 or mPAP &gt;30</td>
<td>8 (IPF=1)</td>
<td>Open label</td>
<td>All ↓ PVR, mPAP Epo ↓ O₂ CCB ↓ BP</td>
</tr>
<tr>
<td>Ghofrani,41 Lancet 2002</td>
<td>iNO, IV epoprostenol or sildenafil</td>
<td>Pulm fibrosis</td>
<td>mPAP ≥35</td>
<td>16 (IPF=7)</td>
<td>Open label</td>
<td>All ↓ PVR, Epo ↓ O₂ Sildenafil ↑ O₂</td>
</tr>
<tr>
<td>Krowka,[abstract] 2007</td>
<td>Inhaled iloprost</td>
<td>IPF</td>
<td>PASP ≥35 or mPAP ≥25</td>
<td>51</td>
<td>DB-RCT</td>
<td>No change in 6MWT, exercise O₂, WHO class in 12 weeks</td>
</tr>
<tr>
<td>King,42 AJRCCM 2008 BUILD-1</td>
<td>Bosentan</td>
<td>IPF</td>
<td>n/a</td>
<td>158</td>
<td>DB-RCT</td>
<td>No change in 6MWD at 12 months. Trend toward delaying time to death or disease progression</td>
</tr>
<tr>
<td>King,43 AJRCCM 2011 BUILD-3</td>
<td>Bosentan</td>
<td>IPF mild, biopsy proven</td>
<td>n/a</td>
<td>616</td>
<td>DB-RCT</td>
<td>No delay in time to death or disease progression</td>
</tr>
<tr>
<td>Raghu,45 Annals 2013 ARTEMIS-IPF</td>
<td>Ambrisentan</td>
<td>IPF</td>
<td>n/a</td>
<td>494</td>
<td>DB-RCT</td>
<td>Stopped early for lack of efficacy and possible ↑ risk of disease progression</td>
</tr>
<tr>
<td>Collard,47 Chest 2007</td>
<td>Sildenafil</td>
<td>IPF</td>
<td>mPAP ≥25 or PASP ≥35</td>
<td>14</td>
<td>Open label-RCT</td>
<td>57% improved 6MWD of 20% at 3 months</td>
</tr>
<tr>
<td>IPFnet,48 NEJM 2010 STEP-IPF</td>
<td>Sildenafil</td>
<td>IPF</td>
<td>n/a</td>
<td>180</td>
<td>DB-RCT</td>
<td>Did not meet 20% change in 6MWD at 12 or 24 weeks. Improvement in sob and QoL</td>
</tr>
<tr>
<td>Han,49 Chest 2013 (STEP-IPF post-hoc analysis)</td>
<td>Sildenafil</td>
<td>IPF</td>
<td>Echo with RV dysfunction</td>
<td>119</td>
<td>DB-RCT</td>
<td>Improved preservation of 6MWD</td>
</tr>
</tbody>
</table>

Adapted from Nathan, 2009.55
cause vasodilation in both nitric oxide-dependent and independent pathways. Riociguat was investigated in a pilot, open-label study of 22 ILD-associated PH subjects (13 with IPF) with the primary endpoints of safety and tolerability. In this study, patients had mPAP >30 mm Hg (mean ± SD 40±10 mm Hg) and PVR >400 dyns·cm⁻⁵ (mean ± SD 656±201 dyns·cm⁻⁵). It showed improvement in 6MWD, cardiac output, and PVR, and no change in mPAP at 12 weeks. Arterial partial pressure of oxygen (PaO₂) decreased by 7±12 mm Hg at 12 weeks, suggesting presence of V/Q mismatch.

In summary, these studies present conflicting results with the use of PAH-specific agents in this population. Several factors may account for this. Some studies included patients with various diffuse fibrotic lung diseases, and response to PAH-specific therapy may differ between different groups. Other studies did not require PH for enrollment or relied on echocardiographic estimates of PASP as a surrogate for PH definition. Moreover, specific IPF patient subgroups most likely to benefit from vasodilator therapy have not been properly identified and studied. Finally, appropriate trial design and endpoints have not been determined for this entity.

Current guidelines discourage the use of PAH-specific therapy in IPF patients.1,13,34 Benefit of PAH-specific drugs in patients with PH-IPF has not been proven. Prospective, randomized, placebo-controlled trials evaluating IPF patients with hemodynamically proven PH and/or evidence of right heart failure by echocardiogram need to be completed before these therapies can be universally endorsed and adopted. Appropriate patient subgroups will need to be identified and targeted (eg, disproportionate PH), in whom PH likely contributes significantly to exercise limitation and morbidity. Moreover, appropriate trial endpoints will need to be agreed upon.

Finally, lung transplantation should be considered in the appropriate IPF patients with progressive lung disease. Five-year post-transplantation survival in IPF patients is estimated to be at 50% to 56%.1 Presence of PH does not preclude lung transplantation and is associated with increased mortality while awaiting transplantation. The current Lung Allocation Scoring System of the United Network for Organ Sharing increases priority for patients with PH in the setting of parenchymal lung disease.51 However, presence of PH also affects post-transplant outcomes with increased risk of primary graft dysfunction,52 perioperative mortality, and postoperative mortality.57

CONCLUSION
In conclusion, PH is a common complication of IPF. The diagnosis of PH-IPF is challenging, as symptoms are nonspecific. Presence of clinical deterioration without progression of underlying parenchymal lung disease justifies further diagnostic testing. Echocardiographic findings of RV dysfunction, RV dilation, and increased RV-LV diameter ratio may suggest presence of PH-IPF. RHC is the gold standard for the diagnosis of PH-IPF, and should be considered when it is likely to influence clinical decision making. Presence of PH-IPF is associated with increased risk of mortality and worse outcome. Therapeutic considerations may include treatment of hypoxemia, treatment of underlying comorbid conditions, and lung transplantation. The application of PAH-specific therapies for PH-IPF is of uncertain benefit and needs further evaluation.

References
Hypoxic Pulmonary Vasoconstriction and Chronic Lung Disease

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Hypoxic pulmonary vasoconstriction (HPV) is a fundamental attribute of the pulmonary circulation, which has fascinated cardiopulmonary physiologists and clinicians since its definitive description in the cat in 1946 and in humans 1 year later. It was immediately appreciated that this response to local alveolar hypoxia and hypercapnia, either alone or in combination generally occurring as result of regional hypoventilation, acts to redirect pulmonary blood flow to areas of better ventilation with their higher alveolar PO2 and lower PCO2. In this fashion, HPV and hypercapnic pulmonary vasoconstriction (HCPV) are potent mechanisms to better match regional perfusion (Q) to alveolar ventilation (Vspecies) and so enhance gas exchange efficiency. If an area of regional hypoventilation is small in relation to the total pulmonary vascular bed, there is little to no increase in pulmonary artery (PA) pressure. When there is more global alveolar hypoxia, such as at high altitude or more extensive hypoxia with or without hypercapnia in diffuse parenchymal and airways disease, HPV still operates to optimize V/Q matching. However, with more of the vasculature undergoing constriction it is less effective in this function and results in increased pulmonary vascular resistance (PVR) and pulmonary hypertension (PH).

The presence and contribution of HPV to V/Q matching and PH in chronic lung diseases (World Health Organization [WHO] Group 3) and the extent to which it might be modified as part of treatment in this setting is not easily assessed. This is due to the fact that other changes in the vasculature in these conditions also increase vascular resistance. Depending on the disease and its duration and severity, these include physical destruction and loss of vascular bed with a decrease in total perfused cross-sectional area, hyperinflation such as with emphysema, reduction in local tonic vasodilator generation and/or increase in vasoconstrictor mediator production, and remodeling of existing vessels with increased smooth muscle mass and perivascular thickening leading to luminal narrowing.

In this review, the present understanding of HPV in the normal and diseased lung will be discussed with the goal of understanding its contribution to WHO Group 3 PH and its potential to be targeted therapeutically or be altered by treatments for these conditions.

Key Words:—arterial hypoxemia, high altitude, hypercapnia, hypoxia, normoxia

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Disclosures: Dr Swenson reports financial relationships with Cardeas, Boehringer Ingelheim, and Novartis.

CHARACTERIZATION OF HPV

Increases in PVR and PA pressure on ascent to high altitude or exposure to normobaric hypoxia universally occur in humans and other mammals. HPV can be detected with elevations in altitude as low as 1600-2500 m or with reductions in FIO2 to 0.15-0.18. The magnitude of HPV (Figure 1) can vary almost 5-fold among healthy individuals, and among species (Figure 2) in part related to total pulmonary vascular smooth muscle and with duration of hypoxia (Figure 3) from minutes to several days. HPV is the earliest mechanism that elevates PA pressure and PVR with hypoxic or high-altitude exposure. Ultimately, other mechanisms (perhaps partly in reaction to the first elevation of pressure initiated by HPV along with greater cardiac output) such as activation of pressure-independent hypoxia-sensitive inflammatory and proliferative pathways may contribute to sustained PVR elevation and vascular remodeling. The process of remodeling is initiated as early as several hours at the level of new gene transcription, such as for collagen and other growth factors, and is generally established within days to weeks of continuous alveolar hypoxia.

The ability to reverse the acute effects of HPV by restoration of normoxia progressively diminishes with sustained
hypoxic exposure. This decline in reversibility has been demonstrated as early as 8 hours\textsuperscript{9} and progressing through 1 to 3 days,\textsuperscript{15,16} (Figure 4) and becomes more pronounced after 1 to several weeks of hypoxic exposure.\textsuperscript{8,17,18} Although changes in inspired oxygen remain widely used to assess HPV, changes in arterial oxygenation and acid-base status always follow an alteration in inspired oxygen, so that systemic effects such as changes in central nervous system (CNS) and autonomic nervous activity might also contribute to the final pulmonary vascular response. It would be useful to employ a truly selective HPV inhibitor or stimulator in vivo rather than use changes in inspired oxygen, but all available pulmonary vasoactive agents have actions elsewhere in the circulation and brain, making them less than ideal for this purpose.

Lowland species with stronger acute HPV tend to develop greater PH with chronic hypoxia than animals with weaker HPV.\textsuperscript{12} Whether humans with stronger HPV develop greater PH with chronic hypoxia or other conditions predisposing to PH has never been studied, but such a characteristic might underlie those often labeled as having “out-of-proportion” hypertension in the face of subsequent development of obstructive sleep apnea, heart failure, emphysema, and fibrotic lung disease. These conditions are more prevalent in older patients, and the impact of aging on HPV is also unknown.

The critical $\text{PO}_2$ at the level of the pulmonary arteriolar smooth muscle which initiates HPV in a lung region or the whole lung is a summation of the effects of alveolar $\text{PO}_2$ as set by inspired $\text{PO}_2$ and the ventilation-perfusion ($V_a/Q$) ratio, the bronchial arterial $\text{PO}_2$, and the mixed venous $\text{PO}_2$.\textsuperscript{3} Because the bronchial arterial circulation perfuses the vaso vasorum of the pulmonary arteries and arterioles, systemic arterial $\text{PO}_2$ will also influence HPV. Separate perfusion of the bronchial artery in the sheep with deoxygenated blood, while alveolar $\text{PO}_2$ and systemic $\text{PO}_2$ were held constant, led to an increase in PA pressure.\textsuperscript{19} In animal studies in which it is possible to control and hold systemic arterial and alveolar $\text{PO}_2$ constant, reductions in mixed venous $\text{PO}_2$ sensed in the PA cause vasoconstriction.\textsuperscript{20,21} The importance of mixed venous $\text{PO}_2$ as a factor in HPV may be magnified with exercise, when mixed venous $\text{PO}_2$ falls to very low tensions as a result of high tissue oxygen extraction and greater arterial hypoxemia than at rest, but of the 3 contributions mixed venous $\text{PO}_2$ likely has the least influence.

**MECHANISMS OF ACUTE HPV**

HPV is a complex process with elements of its expression arising from multiple points in the neuro-cardiopulmonary axis, with variation in intensity and mechanisms over time.\textsuperscript{22} In addition to the intrinsic hypoxic response of the pulmonary vasculature that can be elicited in isolated pulmonary vascular smooth muscle cells and vessels, there are numerous extrinsic modulating influences sensitive to oxygen in vivo that include the vascular endothelial cells, red cells, chemoreceptors, autonomic nervous system, and lung innervation. The pulmonary circulation response to hypoxia is characterized by contraction of smooth muscle cells of the small pulmonary arterioles and veins of diameter less than 900 $\mu$m; the veins account for approximately 20% of the total increase in $\text{PVR}$.\textsuperscript{23,24} At a regional level within the lung vasculature the magnitude of HPV may not be equivalent in all areas or static over time.\textsuperscript{25–28} As a consequence of this

**Figure 1.** HPV variability as assessed by PA systolic pressure response in normal humans to 4 hours of moderate hypoxia. Subjects noted by solid lines are subjects susceptible to HAPE and show exaggerated HPV, while subjects without HAPE susceptibility (interrupted lines) have lower HPV. (Grunig et al. *J Am Coll Cardiol*, 2000.)
unevenness of regional HPV, some areas of the vasculature may be more perfused than others if they have a lower HPV response. This appears to be the case in those with a stronger global HPV response and susceptibility to high altitude pulmonary edema (HAPE). Although it is not generally thought that hypoxia acts at the microvascular or acinar level, pulmonary capillary endothelial cells respond to hypoxia with membrane depolarization, and this signal is propagated upstream and possibly downstream to resistance arterioles and venules. As yet, no evidence has been found for capillary constriction with hypoxia, despite evidence that other vasoconstrictors are active at this level and in surrounding parenchymal perivascular cells that contain actin and myosin microfilaments.

HPV in intact animals and humans appears to be fully expressed within 6 to 8 hours and has several temporal components. The first occurs within 5 minutes with a half-time of about 30-90 seconds. A second phase of greater pressure elevation (almost double) is evident in humans and plateaus at 2 hours. In animal studies, further elevation of pressure develops over the next 6 to 8 hours. This has been confirmed in studies of isolated pulmonary arteries, lungs, or vascular smooth muscle cells showing a third phase taking upward of 8 hours. The mechanisms behind these differing time phases and differences between in vivo and isolated lung and vessel investigations have not been well studied, but the isolated vessel studies suggest the first phase is intrinsic calcium-dependent smooth muscle contraction, with the later phases representing the summation of numerous other modulating influences acting on the smooth muscle in a calcium concentration-independent fashion as discussed below. All of these differing hypoxic responses are fully and immediately reversible with return to normoxia if hypoxia is not extended beyond several hours.

**HPV at the Level of the Vascular Smooth Muscle**

There are several mechanisms involved in HPV that are activated in parallel or sequentially, leading to a critical increase of intracellular calcium and/or an enhanced calcium sensitivity of the actin-myosin that initiates contraction, a response opposite to that which occurs in the systemic vasculature. Intracellular calcium concentration is increased by hypoxia-mediated inhibition of several potassium channels, leading to membrane depolarization and extracellular calcium entry through L-type channels, and a release of calcium from the sarcoplasmic reticulum (SR), with further influx through store-operated calcium channels (SOC), receptor-operated calcium channels (ROCC), and transient receptor potential channel 6 (TRPC6). Figure 5 depicts the very complicated multiple pathways by which intracellular calcium in pulmonary vascular smooth muscle is quickly altered by hypoxia to initiate HPV. In addition, sensitivity to calcium of the contractile elements is enhanced via a hypoxia-induced increase in Rho-kinase activity. The change in oxygen tension that stimulates these components of HPV is signaled by an alteration in the redox status of the smooth muscle cells. Whether an increase or a decrease of reactive oxygen species (ROS) is responsible for HPV signal transduction is still under debate, but a stronger case is emerging that hypoxia increases mitochondrial ROS generation as an upstream signal for HPV. It is clear that high-altitude exposure increases stable circulating markers of ROS production, and persons with higher HPV appear to generate more ROS and less bioactive vasodilating nitric oxide (NO) species across the lung.

**Endothelium-Dependent Modulation of HPV**

The pulmonary vascular endothelium generates a variety of vasoactive medi-
ators that act in a paracrine fashion on the surrounding vascular smooth muscle cells. These include NO and prostacyclin as vasodilators, and endothelin-1 acting as a vasoconstrictor via binding to endothelin-A receptors and a vasodilator by binding to endothelin-B receptors causing NO release.\textsuperscript{36} Isolated human PA endothelial cells exposed to 3% oxygen produce more hydrogen peroxide and thus may also be a source for ROS that initiate HPV.\textsuperscript{40} The endothelium also produces carbon monoxide (CO) via heme-oxygenase-2,\textsuperscript{41} which is upregulated by hypoxia.\textsuperscript{42,43} CO dilates vessels by activating guanylate cyclase to generate cyclic guanosine monophosphate (GMP) in a manner similar to NO. Hydrogen sulfide (H$_2$S), a strong reducing agent, produced in hypoxia is vasoconstricting in the pulmonary circulation by several not yet fully quantified mechanisms.\textsuperscript{44} It should be noted that many of these “gaso-transmitters” alter the concentrations of each other, making it difficult to assess the contribution of each to HPV modulation.\textsuperscript{45,46}

**Erythrocyte-Dependent Modulation of HPV**

Red cells may contribute to HPV and pulmonary pressures in several ways. Although hypoxia-mediated decrease in deformability might reduce flow and increase measured vascular resistance,\textsuperscript{47,48} direct measurements of human and other mammalian red cells over a range of PO$_2$ from 120 to 47 mm Hg show no evidence of significant deformability changes.\textsuperscript{49} With elevations in hematocrit with altitude, pulmonary vascular pressures increase. This is partly due to increased blood viscosity and direct increases in lung vascular resistance as shown by hemodilution studies at high altitude in patients with chronic mountain sickness\textsuperscript{50} and in animal studies.\textsuperscript{51} Red cell-mediated changes in PVR with hypoxia represent a balance between those effects that are vasodilating and others that are vasoconstricting. Direct endothelial cell NO scavenging by oxyhemoglobin\textsuperscript{52} and ROS generation by hypoxic red cells\textsuperscript{53} will enhance HPV. In contrast, the oxygenation dependent behavior of red cells and hemoglobin that lead to s-nitrosothiol release\textsuperscript{54} and NO generation from nitrite with hemoglobin desaturation\textsuperscript{55} will blunt HPV. Additionally, deoxygenated red cells also release adenosine triphosphate (ATP), which activates endothelial cell NO production via purinergic receptor binding\textsuperscript{56} and so act in a vasodilating fashion. Finally, recent evidence that red cells themselves express the endothelial isozyme of nitric oxide synthase (eNOS) and are able generate NO that escapes intracellular hemoglobin binding\textsuperscript{57} needs to be considered. Similar to the various and sometimes competing interactions of endothelial cell vasoactive mediators on HPV, the contribution of red cells is similarly complicated and the net result on PVR may vary depending on the degree and duration of hypoxia.

**Neurohumoral-Dependent Modulation of HPV**

The lung vasculature is innervated by sympathetic noradrenergic fibers from the large conduit arteries and veins down to 50 mm vessels in larger species such as man and dogs, but much less so in smaller species.\textsuperscript{58} In addition to release of norepinephrine with sympathetic activation causing vasoconstriction via alpha-1 adrenergic receptors on vascular smooth muscle, there is release of other opposing vasodilating neurotransmitters such as neuropeptide Y and vasoactive intestinal peptide.\textsuperscript{58} Additionally, there is opposing NO-dependent vasodilating parasympathetic innervation.\textsuperscript{59} Arterial PO$_2$ is gauged by the peripheral chemoreceptors, which project afferents to the medullary cardiovascular control areas in the brain stem in addition to the respiratory control center, activating both...
parasympathetic and sympathetic outflow to the lung. Denervation of the carotid bodies and loss of afferent input from the peripheral chemoreceptors increases HPV.⁶⁰,⁶¹ The efferent arc of this response is not well defined but is conveyed by the vagus nerve. Vagotomy reduces HPV.⁶²,⁶³ Studies using atropine and propranolol suggest that vasodilating parasympathetic activity is more dominant than sympathetic activity in HPV inhibition.⁶³,⁶⁴ Other data suggest a stronger sympathetic contribution.⁶⁵

In regard to neurohumoral mediation of HPV, susceptibility to HAPE is characterized by a very exaggerated HPV⁶⁶ and a much greater generalized sympathetic nervous system activation to hypoxia.⁶⁷,⁶⁸ However, not all studies find evidence for neural modulation of HPV.⁶⁹ The reason for this discrepancy is not clear, but those studies finding no effect on HPV have employed receptor blocking drugs rather than neural pathway interruption. It is entirely possible that peripheral chemoreceptor-mediated modulation of HPV may involve other neurotransmitter release via the lung innervation besides catecholaminergic or cholinergic agonists as described above. In humans, the association of stronger hypoxic ventilatory response (HVR), which is almost wholly a peripheral chemoreceptor mediated response, with weaker HPV supports the majority of the animal work.⁷⁰

The pulmonary vasculature expresses adrenergic and cholinergic receptors, as well as other receptors, including those for thyroxine, angiotensin II, adenosine, natriuretic peptides, and estrogen. Thus it can respond to circulating vasoactive mediators with dilation by epinephrine via beta-2 receptors,⁵⁸ estrogens,⁷¹ and natriuretic peptides,⁷² and constriction with angiotensin,⁷³ adenosine,⁷⁴ and thyroxine.⁷⁵ The full neurohumoral component of the lung vascular response to hypoxia is often neglected in discussions of HPV.

**Other Modulating Influences on HPV**

Individual genetic background⁷⁶-⁷⁸ and a history of familial susceptibility to HAPE or PH⁷⁹-⁸¹ also contribute to the strength of HPV. Acid-base status and carbon dioxide have a considerable influence on HPV, with alkalosis and hypocapnia both diminishing HPV and hypercapnia increasing HPV.⁸²,⁸³ Thus subjects with stronger ventilatory responses to hypoxia will not only maintain higher alveolar PO₂, but also will have less HPV due to their greater hypoxic alkalemia at any given altitude or FIO₂. Increasing lung volume by positive end-expiratory pressure in the range of 8-10 cmH₂O does not reduce HPV.⁸⁴ Pre-existing high arterial wall tension also diminishes HPV.⁸⁵ Lastly, animal studies with low-grade infection or inflammation show that circulating and locally produced inflammatory leukotrienes, thromboxanes and cytokines, (ie, tumor necrosis factor, interleukin-6),⁸⁶-⁸⁹ or activation of their receptors in the vasculature⁹⁰ appear to modulate HPV (both negatively and positively).

**Hypoxia-Regulated Gene Transcription Factors and HPV**

The study of HPV continues to identify new sensing, signaling, and effector mechanisms and pathways. The most recent are the hypoxia-inducible factors (HIFs), transcription factors that alter the gene expression over 1000 genes involved in promoting tolerance to hypoxia.¹⁰ In this fashion, hypoxia and inflammation may be inextricably linked in chronic lung diseases. In 2 rat strains with differing pulmonary hypoxic
responses, HIF-1 activity and HIF-mediated protein expression were higher in the strain with greater PH. In contrast, mice with heterozygous HIF-1 alpha deficiency have weaker acute and chronic hypoxic responses in isolated pulmonary vascular smooth myocytes and pulmonary vessels than wild-type mice. Further supporting pharmacological evidence for HIF-1 alpha mediation of HPV was demonstrated in mice by reduction in hypoxic PH with digoxin, a known inhibitor of HIF-1 alpha transcriptional activity. At present it is not fully clear how HIF-dependent gene transcription affects HPV, but it likely involves upregulation of TRPC on the vascular smooth muscle cell membrane and alterations in pulmonary vascular smooth muscle calcium signaling. Iron is emerging as a critical element in HPV and pulmonary vascular changes with hypoxia. Iron supplementation and iron chelation reduce and increase HPV respectively, possibly via altered HIF metabolism involving prolyl hydroxylases, the O2-sensitive enzymes that degrade HIF and require iron. HIF-mediated gene transcription also drives much of the longer-term remodeling of the vasculature.

RELEVANCE OF HPV IN HEALTH

At low altitudes where humans evolved, it would appear that the sensitivity to oxygen of the lung vasculature evolved along with HCPV as mechanisms to shift blood flow from poorly or nonventilated lung regions with localized airway or airspace pathology in post-fetal life to better ventilated and healthy areas as elegantly advanced by von Euler and Liljestrand in their landmark paper. Based on whole lung pulmonary vascular responses to changes in alveolar PO2 and PCO2, Dorrington et al modelled that improvements in V_A/Q mismatching and gas exchange by HPV are most important in the lower range of V_A/Q (0.01 to 1.0), and that HCPV has its greatest impact in the V_A/Q ratio of 1 to 100. The ability of both HPV and HCPV to divert blood flow and minimally raise PA pressure are more effective when the area of V_A/Q mismatching is smaller. From an evolutionary perspective, HPV may have conferred a survival (and ultimately a reproductive) advantage for individuals with severe pneumonia or thoracic trauma with acute pneumothorax by limiting the degree of severe life threatening shunt-induced hypoxemia. This may still be the case even in the modern clinical era of effective antibiotics and surgery before patients can be treated. Alternatively, others have argued it may be simply a vestige of fetal existence. In this regard, HPV maintains a high vascular resistance to limit blood flow in the nonventilated lung (in combination with a patent ductus arteriosis and foramen ovale) to allow an 80% to 90% right to left shunt to provide more blood flow to the placenta and better oxygenated blood to the developing brain. However, many other aspects of the fetal lung also contribute to higher PVR, including its liquid-filled nonventilated high volume...
state, lack of surfactant, relative hypercapnia and acidosis, a limited slower growing vascular bed relative to the faster growing airway and parenchymal structure, lesser endothelial vasodilator generation, greater endothelial vasoconstrictor production, and lack of bronchial epithelial nitric oxide (NO) generation. In fact, HPV in the fetal lung does not appear until the middle of the third trimester of gestation. Thus, it would appear to reduce pulmonary vascular resistance (PVR) and prepare the pulmonary circulation to accommodating the entire cardiac output at birth as the ductus arteriosis closes and the lungs are ventilated. Consequently, it would appear to reduce HPV in the fetal lung does not appear until the middle of the third trimester of gestation. Thus, it would appear to reduce pulmonary vascular resistance (PVR) and prepare the pulmonary circulation to accommodating the entire cardiac output at birth as the ductus arteriosis closes and the lungs are ventilated and assume gas exchange duties from the placenta. In this sense, HPV should perhaps more correctly be renamed "oxygen-dependent vasodilation." If strong HPV is an evolutionary advantage in utero, then one might predict a fetal survival disadvantage in Tibetans, who have much lower HPV as adults than other populations. Yet, birth rates and neonatal survival in this population exceed those of newcomers to high altitude.

**RELEVANCE OF HPV IN CHRONIC LUNG DISEASE**

In the setting of chronic lung diseases, several questions regarding HPV are relevant. The first is whether it is present and what is its magnitude. The second is how useful is HPV in maintaining as optimal state of gas exchange as possible. The third is what benefit or harm is realized with therapies that either directly alter HPV or alter it as a consequence of targeting some other aspect of the disease.

In answering the first and second questions, if the model of chronic global hypoxia such as that occurring with long-term high-altitude exposure is any answer, then the finding that after several weeks at high altitude there is little pulmonary vasodilation with breathing oxygen would suggest HPV should not be present to any great extent in chronic hypoxic lung diseases.

Some patients with chronic obstructive pulmonary disease (COPD) and chronic bronchitis given high levels of inspired oxygen acutely show deterioration in $V_A/Q$ matching suggestive of inhibition of HPV, but this has not been shown in every case. Although these data and data from other studies have been used to support the idea that HPV is contributing to the high vascular tone, in studies with right heart catheterization there is minimal reduction in PA pressure with supplemental oxygen therapy either acutely or chronically in most patients. This apparent paradox might be explained either by there being only small regions of lung having any HPV, such that gas exchange deterioration still takes place, but reduction in overall PA pressure is minimal. A second possibility is that simultaneous increase in local carbon dioxide brought about by an increase in blood flow with release of HPV in these areas leads to counteracting HCPV and limits the fall of pulmonary artery pressure. Despite the equivocal salutary effects of short-term oxygen, it is clearly established that chronic supplemental oxygen extends life in hypoxemic COPD patients and that this is associated with a mild improvement in pulmonary hemodynamics in those using continuous oxygen. In patients exhibiting a significant drop in mean PA pressure of $>$5 mm Hg the benefits were greatest.

The benefits of oxygen therapy are multiple and stem largely from improvements in systemic oxygenation. However, the pulmonary vascular effects of oxygen in the long run may be related to HPV in much the same way that all models of chronic hypoxic PH in animals and in humans relocating from high altitude to sea level ultimately show regression of PH after return to normoxia.

In interstitial lung disease the story is different. Two studies have shown no significant vasodilator response or change in $V_A/Q$ matching with 100% oxygen and chronic home oxygen administration does not alter mortality in fibrotic lung diseases. Therefore, from these data it appears that HPV does not contribute greatly to PH in interstitial lung disease.

HPV can be decreased for treatment purposes by a variety of pharmacological agents that act on many of the endothelial cell-derived modulators of PVR, signal transduction pathways, and gene transcription discussed above, including NO, nitrates, calcium channel blockers, phosphodiesterase 5 inhibitors, endothelin receptor blockers, prostacyclin analogs, soluble guanylate cyclase (sGC) activators, angiotensin converting enzyme inhibitors, and some carbonic anhydrase inhibitors, such as acetazolamide. While these drugs certainly inhibit HPV at high altitude and some are quite useful to prevent and treat HAPE and high-altitude PH, it must be appreciated that none of these agents are truly specific HPV inhibitors, except perhaps for acetazolamide. Their pressure-lowering effects act on intracellular calcium signaling, mediator release, or receptor engagement, some of which may be common to HPV.

Several of these drugs that have been tested in patients with COPD and idiopathic pulmonary fibrosis (IPF) (as will be discussed in the 2 accompanying articles in this issue) may impair gas exchange efficiency by inhibiting HPV and/or by general vasodilation more in areas of shunt or low $V_A/Q$. For instance, with oral sildenafil in COPD, PA pressure is lowered at equivalent exercise intensity, but in some arterial $P_O_2$ falls. In those that derive an exercise and pressure-lowering effect, the drop in oxygenation could be likely prevented by small increases in their supplemental oxygen flow rate. Whether this is a tenable approach and might increase exercise capacity requires formal testing. (Note added in proof: A recent study by Blanco et al. showed no benefit of sildenafil to a comprehensive pulmonary rehabilitation program in exercise endurance or quality of life.)

Lastly, the adverse effect of giving these agents orally might be mitigated by giving them by inhalation in order to vasodilate preferentially in the better ventilated regions and not worsen $V_A/Q$ mismatch such as with ioprost.

**CONCLUSION**

The search for more potent and selective vasodilators for the treatment of nonhypoxic forms of PH grows apace, and it is likely that most will have the ability to inhibit HPV. It may be useful in selected patients without an obvious ventilatory limitation at maximal exercise to...
measure how much both oxygen and medications lower PA pressure and restrict their use to those with reductions in PVR associated with increased functional capacity or decreased dyspnea while adding or increasing supplemental oxygen as needed to maintain acceptable arterial oxygenation levels.

There is considerable diversity among WHO Group 3 PH patients and within the individual diagnostic subsets comprising this group. While HPV may play a variable role in the pathogenesis of PH in Group 3 patients, and treatment of hypoxia remains an important therapeutic consideration, the heterogeneity of this population poses significant challenges for development of effective treatment.

Multiple pathways associated with HPV, HCPV, other V_{A}/Q matching mechanisms, hyperinflation, inflammation, vascular remodeling, and parenchymal loss contribute to the development of PH and pose significant challenges for identification and evaluation of potential therapeutic agents. Understanding these mechanisms and identifying patient groups where similar pathways predominate is a critical component in the evolution of treatment for WHO Group 3 PH.

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COPD, IPF, and Pulmonary Hypertension: A Clinician’s Dilemma

On October 9, 2013, a group of experts met by telephone to discuss PH in the setting of COPD and IPF. The group consisting of guest editor of this issue Jeffrey Edelman, MD, Head, Lung Transplant Program VA Puget Sound Health System, University of Washington; Deborah J. Levine, MD, Director, Pulmonary Hypertension Center, University of Texas Health Science Center at San Antonio; James Klinger, MD, Director, Rhode Island Hospital Pulmonary Hypertension Center; and Robert Schilz, DO, PhD, Director of Pulmonary Vascular Disease and Lung Transplantation, University Hospitals, Case Medical Center; provided perspective and insight into how clinicians can approach these patients most effectively.

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Dr Edelman: I thought it would be reasonable to discuss: when to consider PH in COPD and IPF; the approach to evaluation (such as when to obtain right heart catheterization); and other comorbidities to consider when PH is present in the setting of these conditions as well as the impact of coexistent COPD with pulmonary fibrosis. Additionally, we shall discuss whether or not PH is, in and of itself, an indication for treatment or more of an indicator of prognosis in these patients.

Dr Schilz: This topic was discussed in depth at the World Symposium for Pulmonary Hypertension in Nice, France this year, summarizing this topic in a way that a lot of us think about WHO Group 3 disease. I think that we know that there are a lot of data and information on what typical elevations of pulmonary pressures are in the major diseases that comprise Class 3, especially COPD, IPF, and sleep apnea. And in the grand scheme of things, those pressures are typically pretty modest if you go back and look at a number of the very key and important studies.

Dr Edelman: Knowing that these patients are at risk for pulmonary hypertension and knowing the size of these populations, I’d like to start by asking when you think about pulmonary hypertension in this population.

Dr Schilz: I think we can take a lot of lessons from the literature in helping us understand about PH and COPD. A widely quoted study by Chaouat, sampling almost 1,000 patients consistently reported that mean pulmonary pressures were generally less than 20, even in patients with advanced COPD and respiratory failure. And only about 3 percent of patients had means that typically were over 35. And even less than that had means that were typically in the 40 to 50 range or greater than we usually see in PAH patients. Similarly, findings are reported in transplant or lung volume reduction patient populations...So in general, significant elevation in pulmonary pressures, which usually characterize our PAH patients, are typically not seen in COPD.

Dr Klinger: I think that’s an important point to focus on. One of the ways to put it in perspective is that if we look at the average mean PA pressure in registries of people that have Group 1 pulmonary arterial hypertension, we’re usually talking about values in the 50 to 55 mm Hg range. Usually in the chronic lung diseases, people get excited or at least interested in pulmonary arterial pressures when we’re seeing systolic PA pressures that are 55 to 60 mm Hg, which gives them a mean PA pressure, as Bob was saying, around 25 or 30. So they’re really kind of separate groups.

That is to say, most of the PH that we see associated with chronic lung disease is right at the borderline of the cutoff for a definition of pulmonary hypertension, whereas most of the pulmonary hypertension we see in Group 1 is twice as high as the mean cutoff level for pulmonary hypertension.

Dr Levine: I agree, Jim. However, when you look at patients with end-stage lung disease (more with ILD than COPD) when they come for lung transplant evaluation, there is a small proportion who come with very, very high mean pulmonary artery pressures. Most of them have mild or even moderate pressures as you are alluding to, but this small but significant portion of patients have severe pulmonary hypertension. This group of patients is one group that can really be separated out from the other patients with end-stage lung disease and we may treat them differently based on that.

Dr Schilz: It is interesting, however, that in spite of that, historical epidemiology continues to underscore the fact that even modest amounts of elevations of pressure in the lung, when associated with advanced COPD or IPF are associated with worse outcomes.

Dr Levine: Absolutely.

Dr Schilz: The existing data summarized point to 2 important trends. First, that patients with COPD and PH appear to comprise 2 different populations: one with very modest (by PAH standards) pressures and one with mean...
pulmonary pressures approaching that typically seen in PAH populations. Second, that having elevated blood pressures in the lung, in the presence of COPD seems to be associated with a worse outcome. I think the latter has driven therapeutic trials in this area to date that have been tried in these groups so far, quite honestly, unsuccessfully.

Dr Edelman: I think we all see enriched populations of patients with more advanced disease. But if you’re treating patients outside of the context of a PH program or a transplant program or an ILD program, which patients should you think about evaluating for pulmonary hypertension and how? I mean, are there red flags that would lead one to say, “Hey, I should start and get an echo for this person,” or do we get them for all patients? How do we decide when to start thinking about PH in these patients?

Dr Levine: We can use pulmonary function tests to help us in this regard. One of the values we can look at in these patients is the DLCO. If there is a disproportionate decrease in the DLCO (as compared to the rest of their pulmonary function tests) and they are more hypoxemic than you feel they should be based on other indices (CT scan, lung volumes, VQ scan), it may trigger you to consider the pulmonary vascular disease playing a more significant role.

Dr Schilz: Yes, I think that’s a great point and suggests another topic that I wanted to add—that was the entity that all of us have seen over time that seems to find its way into pulmonary hypertension clinics—the fibrotic COPD patient—described in a systematic way in Chest by Mejia et al. in 2009. These patients have abnormally low DLCO, profound parenchymal destruction and significantly elevated pulmonary pressures with a modestly affected FEV1. From my perspective these patients are disabled more than I think they ought to be, based on their FEV1s, based on their conditioning, and so forth. They appear much more like a patient with PAH. To answer your question directly, if someone is more dyspneic than you think they ought to, they perhaps deserve a different look.

Dr Klinger: I think that’s the key that we would want to get out as a message. That is to say, the time to evaluate the patient is not so much dependent on their echocardiogram or even their estimates of their PA pressure, but rather how those numbers correlate with their performance. Patients with mild lung disease and high PA pressures that are associated with dyspnea that’s difficult to explain are the ones that we really get concerned about. The issue often is whether the pulmonary hypertension is part of the chronic lung disease, or an independent disease process, or as I think most of us are coming around to, an exaggerated pulmonary hypertensive response to an underlying lung disease. We ask ourselves, do those people have the ability to be improved upon if we treat their pulmonary hypertension. When their dyspnea becomes out of proportion to their underlying lung disease, I think that’s when most of us start looking for secondary causes and frequently pulmonary hypertensive disease.

Dr Schilz: Jim, I couldn’t agree more. Another factor that draws my attention in this population is an abnormal right ventricle. But certainly, we all know the importance of the right ventricle. And any right ventricle that starts getting dilated gets my attention, as well. And again, that’s not a common finding in most COPD patients, even with advanced COPD. So a patient with a performance status that is not explained by their FEV1, coupled with an enlarged RV, in my mind should make us think about pulmonary hypertension.

Dr Klinger: Yes, I think that’s very important. We frequently look for cor pulmonale and if we see it, we get much more concerned about either chronic CO2 retention or nocturnal hypoxemia or other forms of hypoxia that are not well-appreciated. Frequently, we see this in combination with polycythemia or at least elevated hemoglobin levels. That combination really needs to be looked at carefully in such a way that if we can reverse the hypoxia, the hypercapnia, and the underlying polycythemia, a lot of that cor pulmonale and pulmonary hypertension will improve on its own.

Dr Edelman: So one issue there that you’ve touched on is that the first response to seeing evidence of pulmonary hypertension is to think about what other comorbidities may be contributing. These may include, hypoxia, hypercapnia, chronic thromboembolic disease, left heart disease, collagen vascular disease, sleep disordered breathing, and if the patient is still smoking, perhaps carboxyhemoglobinemia. Bob, you also used the term “fibrotic COPD.” I think about that as COPD coexisting with pulmonary fibrosis, particularly that setting where you may have upper lobe emphysema and lower lobe pulmonary fibrosis. In effect you have different hits to the pulmonary vascular bed with “off-setting” impact on lung compliance, so that your spirometry numbers and your lung volume numbers may look relatively normal, but the telling factor is the hypoxemia, the low DLCO, and the poor exercise tolerance.

Dr Klinger: Yeah, this is a very interesting group of patients. Just by coincidence, I literally saw this guy yesterday in the office who had worked out for a professional football team nearly 50 years ago but now is extremely limited. We haven’t had a chance to get all his records yet, but by report, he’s got normal PFT’s. His FEV1, FVC, and TLC are all within 95 to 105 percent of predicted. He has no obstructive defect at all, but he has fibrosis and emphysema on his high res CT scan and his DLCO is 8% of predicted. His RV systolic pressure on echocardiogram is estimated to be 89 mm Hg and, interestingly enough, he’s got a preserved right ventricle.

I think he is kind of a poster child of this disease that has been characterized somewhat as a new entity and that is referred to as combined pulmonary fibrosis and emphysema. This is an unfortunate progression of disease in somebody that’s got underlying emphysema that results in fibrosis of the healthy parenchyma and then, of course,
continued destruction by emphysema of the rest of the parenchyma, leaving essentially very little gas exchange surface and probably very little pulmonary circulation for the blood flow to go through, so they're really in a very bad situation with very little respiratory reserve.

Dr Schilz: These can be very ill patients. But they tend to show up in our clinic just as you and Jim have pointed out. Their PFTs are often modestly down. I see a lot of FEV1s in this group of 60–70%. But as you say, when you look at the CT scan they demonstrate profound parenchymal damage and distortion, and when you look at their performance on exercise and their desaturation with exercise, they're often very hypoxic as well. I think this is a very interesting and unique group, but I think an important group to talk about. It has been characterized and they do tend to show up in specialty pulmonary hypertension clinics.

Dr Klinger: Yes, absolutely.

Dr Schilz: Everyone has brought up several concepts that, I think, may guide the next phase of our discussion. We all understand that typical levels of pulmonary hypertension that accompany pulmonary disease tend to be modest at best, but small subpopulations can achieve pressures typically seen in PAH. Some of these patients may have profound parenchymal lung destruction. This suggests a possible separation of these populations into logical groups based on high vs low mean PAP and significant vs modest parenchymal lung disease.

We all go through the exercise of separating comorbidity from cause in our PAH patients. We know that the importance of separating out coexisting disease with true idiopathic patients is something that we need to do in the setting of PAH. Let us consider the following theoretical COPD patient (not one of these fibrotic COPD patients): a patient with an FEV1 of 70%; no significant emphysema on imaging; expected DLCO; absence of profound exercise desaturation; and a mean pulmonary arterial pressure of 50 or 55 mm Hg. In the absence of left heart disease I think that most of us would suggest that this patient has two diseases: PAH and COPD. This type of discussion comprised at least part of the discussion in the World PAH Symposium. We all recognize that comorbidities exist and that by definition, part of our patient population, if they share risk factors and demographics, will have COPD or ILD, even though they have truly IPAH as well.

Dr Klinger: Yes. I think that's a point worth discussing. In the REVEAL Registry, for example, where patients are referred in from pulmonary hypertension centers, about 18% were reported to have COPD as a comorbidity. So it's definitely out there. I think in the general population, the incidence of COPD is about the same, it's around 12% or so.

Dr Schilz: Exactly.

Dr Klinger: It's possible that there is a higher incidence of COPD comorbidity in Group 1 PAH, although we probably don't have the data to say that. But I think it bears keeping in mind that at least, 1 out of 5 or 6 patients with pulmonary hypertension is going to have COPD. So we are frequently faced with the task of deciphering whether we are seeing a PAH patient with COPD or a COPD patient that has pulmonary hypertension.

Dr Levine: And this may be where these patients with end-stage lung disease and very high pressures come in. They have Group 3 disease, but still have very high pressures. So this is what this special population may be.

Dr Schilz: Yes I agree. These concepts formed the basis of significant discussion at the most recent World Pulmonary Hypertension Symposium in Nice. The literature-based discussion identified groups with very severe lung disease and very high mean PAP as an “out of proportion” group versus an “in-proportion” group (pardon my grammar), and then explored the concept of mild comorbidities in the setting of what truly may be IPAH. This structure led to a very productive discussion, in my opinion.

Dr Levine: It is very important to everyone treating all three types of patients: ILD, COPD, and PAH patients. In terms of evaluation, as well as management, the possibilities of therapies are going to be quite different. So I think it will be very interesting to hear how that discussion at the World Symposium proceeded.

Dr Schilz: The World Symposium consensus statement will be forthcoming and I believe will be useful in this regard. I'd like to turn to a survey, which a number of us filled out, and that was ultimately brought forward in *Respiratory Medicine* in 2010, by one of our colleagues, Omar Minai. And if you'll remember, this was a survey of PH and lung disease. There was a general opinion that PH in the setting of lung disease carried a poorer prognosis. Most people felt that oxygen was important in hypoxic patients. It was interesting that the thought, at least among people who treated PAH, was that there certainly would be some groups that they felt deserved closer evaluation or perhaps deserved treatment.

Dr Levine: It would be very interesting to know the numbers in that, in terms of what people called out of proportion PH. Was that issue brought up in the survey?

Dr Schilz: Yes, it was. And so of the responders, the question paraphrased was, when would you consider prescribing PAH medicines? Obviously this may represent off-label prescription. About 30–40% of people said they would when they had very severe pulmonary hypertension, persistent pulmonary hypertension in spite of oxygen administration, significant functional limitation, or “out of proportion PH” without an obvious qualifier on the degree of PH.

Dr Levine: I think one of the questions is “Do we have a definition for ‘out of proportion’ PH?”
Dr Schilz: Perhaps with the publication of new consensus statements in the upcoming months.

Dr Levine: Okay.

Dr Edelman: I think that’s easier to conceptualize, but harder to define by numeric criteria. But I think it will be important to have that going forward, as it may help to define patients for inclusion in clinical trials, so we can start to evaluate whether there are sub-populations that may benefit from treatment.

Dr Schilz: I think that thresholds as you mention are critical for defining investigation and may be possible utilizing current literature and distributions of pulmonary pressure elevations in the setting of parenchymal lung disease. Resting pressures of less than 25 mm Hg at this time can be excluded as normal. (Note that I have chosen not to discuss exercise pressures, which represent yet another discussion). Jim, you brought up before that mean PAPs of 50 mm Hg or more are unusual but serious. If we start stepping back—a mean of 45, probably significant—a mean of 40 . . . and if we get down to a mean of 35, that’s when you start getting the tail end of the normal distribution of what would be expected in the normal end-stage patient with severe ILD or COPD. These are the kinds of issues that were discussed at the Worlds. And so drawing the line somewhere below 50 but certainly in that 35, 40, or 45 range, I think makes some deal of sense when we know the normal distribution of elevations of pressures that have been seen in the literature.

Dr Levine: But I think that’s definitely progress from where we were previously. If we have at least established a baseline which most people call normal, then this work toward standardization is going in the right direction.

Dr Klinger: I would just caution that there is a very slippery slope here to believe that there is a kind of a cutoff level or a threshold where the pulmonary hypertension is out of proportion and should be thought of as a separate disease. You still have a very high number of patients in that chronic disease population that would fit that threshold and absolutely no data anywhere, at least that I’m aware of, to say that there are situations where you can actually make people better by treating their pulmonary hypertension when it’s associated with chronic lung disease.

Dr Schilz: Jim, that’s a great point. I think ultimately, before we’re done, we should talk a bit about the attempts of treating so far.

Dr Edelman: Before we move to treatment, I want to ask about one other line to draw, so to speak. We talked about mean pulmonary artery pressures quite a bit in thinking about different populations. And a mean pulmonary artery pressure implies that you’ve had a right heart cath. And so in these patient groups, when do we move to right heart catheterization? It may not be everybody and it may not be everybody with an abnormal echo. The question is: are we going to identify patients where there’s going to be some kind of alteration in our approach as a result of a right heart catheterization?

Dr Schilz: Those are great, great questions, Jeffrey. I see a number of patients for advanced surgical options for advanced parenchymal lung disease either transplant or LVRS. These patients in general are cathed because an alteration in the approach may be dictated by elevated pulmonary pressures. It is a routine part of that evaluation. Clearly just the presence of parenchymal lung disease does not justify RHC in all patients. I consider right heart cath when I can’t explain disability and I’m looking for alternate factors—usually in a patient that has an abnormal RV. A lot of these patients may also have multiple risk factors, at least in COPD, for coronary disease. I know that each and every one of you have likely obtained right and left heart catheterization and found 90% LAD occlusions or heart failure that you didn’t expect. These issues can be effectively treated.

Dr Klinger: Bob, that’s a really interesting issue. Normally in our approach to right heart cath for PH, the idea is we’re doing the right heart catheterization with the expectation that when we rule out other causes of elevated PA pressure we’re going to start treatment for PAH. But in the patient with fairly advanced or moderate underlying lung disease, we’re not sure if we’re going to treat the PAH, even if it’s really there on right heart cath.

Dr Schilz: No, you’re right.

Dr Klinger: There is, of course, something else that we might find on the right heart cath, such as diastolic dysfunction, or other diseases that we think would be amenable to other treatments or an explanation for their underlying pulmonary hypertension.

Dr Levine: I agree. We know that in many patients with lung disease, the echo is far off when compared to the right heart catheterization. Remember Dr. Selim Arcasoy’s study on ILD patients at transplant, comparing the echo findings to those with right heart catheterization? The echo pressure was higher in some patients and lower in other patients. So you may use the RHC to not only rule in PH, but also to say, “Hey, there really is no PH here, so we may need to look elsewhere for causes of their severe dyspnea or hypoxemia.”

Dr Schilz: Prognostically, you do have information that says that even if you get PH which is “expected,” that implies a worse course for a patient. That may change your timing on transplant or other interventions, or your perspective on LVRS and so forth. Data from the studies that we’ve done so far do not appear to support the use of PAH drugs in these patients. Patients with very high pulmonary pressures and parenchymal lung disease represent a population that has not been studied rigorously but one that really most urgently deserves careful investigation. Interestingly, some of the experimental initial phases of inhaled nitric oxide are starting to include some of these populations right now.
Dr Edelman: I think in the context of this discussion, one important point is that when we're talking about PH-directed treatment in these groups, what we're really talking about is trying to think about populations for whom clinical trials would be appropriate. We don't really have evidence supporting PH-directed therapy in these population groups at this point. I'm wondering also what the approach is in clinical practice right now. What do we do when we find these patients who we think have PH that’s “out of proportion”? We do a diligent search for other comorbidities and associated conditions. We think about transplant. Do we have a discussion about prognosis? Do we consider PAH drugs or do we look at the evidence and say, “there's not a whole lot of evidence base for treatment.”? There's not much in the way of consensus in clinical practice. I think if you look even at the most recent guidelines for treatment of IPF, there is still a little wiggle room left and there’s a statement that PH treatment may be appropriate for a minority of patients. And the focus is largely on PDE-5 inhibitors, particularly sildenafil based on recently reported results of the STEP-IPF trial. And then the last thing to think about is in the absence of evidence or consensus, do we do empiric trials of treatment for individual patients or is that fair to patients?

Dr Klinger: Yes, so probably not. Not only do we have little information to suggest that most of our therapies are not helpful, but we actually have accruing information to suggest that most of the pulmonary vasodilators that are available now to treat pulmonary hypertension when applied to people that have chronic lung disease are capable of doing harm, both in terms of worsening oxygenation and decreasing quality of life. In fact, there are some fascinating data that's coming out of the recently published ambrisentan for pulmonary fibrosis study suggesting that those people who were treated with ambrisentan actually had worsening of lung function and more frequent hospitalizations. There’s just the reality that not only are we unable to improve our patients with these treatments, but that we can actually make them worse by trying to treat their pulmonary hypertension. So the approach really has to be, I believe, convincing yourself that the person's pulmonary hypertension is not due to their underlying lung disease, and that you really have 2 diseases going on and you’re going to treat them separately. That means for patients with mild pulmonary hypertension in association with moderate to severe lung disease, we really should be looking away from trying to treat these patients' pulmonary hypertension.

Dr Schilz: I agree. I agree 1,000%, Jim. And just to take that ambrisentan data one step further, that study also generated the black box warning on ambrisentan.

Dr Klinger: Right.

Dr Schilz: I think Jim has summed things up nicely. Some patients clearly seem to have 2 diseases. That patient with FEV1 of 75%, their CT isn't bad, their DLCO isn't bad, and they've got mean pulmonary pressures of 55 mm Hg, and they smoked for 15 years: we think that this may represent 2 disease processes and that many of us would treat this as a PAH patient with a comorbidity. A second group was mild PH—the PH which is expected in ILD or COPD has been studied already. The results suggested either no benefit or, as Jim pointed out, potential harm in some patient populations. I think the last patient population, which is the big question mark, is clearly an ill group of patients, one greatly in need of RCTs, and perhaps that group which Jim has mentioned: the patient who displays pressures comparable to PAH patients, well out of proportion to what you’d expect, even considering possible significant parenchymal disease. Maybe this population has 2 diseases, maybe an unusual variant of PAH causing such profound hemodynamic and functional compromise. I think that this group in particular needs to be looked at more carefully.

Dr Edelman: Yes, I think the context that I brought that up was with the notion of sort of defining patient groups, where the PH was greater than expected.

Dr Levine: But I think the fact when you’re talking about management, you’re also talking about management of the diseases in terms of further therapy, even beyond pharmacotherapy. And so when you're looking at treating patients with these severe diseases and with the fact that they do have pulmonary hypertension, whether it be super high or even moderate, that their survival is less, and that you might want to refer them earlier for a different form of therapy, for example, LVRS or transplant. So when you talk about therapy, knowing that they have PH is also very important in the next step you take.

Dr Schilz: No, absolutely. And again, optimizing those sorts of therapies. Obviously, LVRS has a relative contraindication of performance in higher pulmonary pressures. These types of patients certainly need to be seen by centers that have expertise in advanced lung disease, transplantation, advanced therapies, perhaps experimental therapies, as well as the management and evaluation of pulmonary hypertension, which I think is a clear message that we ought to bring out, as well.

Dr Klinger: Jeff, you brought up an interesting topic and that is the discussion of new entry criteria for clinical trials going forward. I'm not sure if that's an issue that you want to discuss in this issue, but there are a lot of different opinions about which patients should be targeted and which patients should be studied for a variety of different information. We can certainly discuss that, but I think it may open up a lot of questions that the practitioner who is trying to treat the patient would not necessarily be looking at. That is to say, some parties may try to design a study that would have the greatest chance of achieving a positive result, but may not answer the question of when do you treat patients that have pulmonary hypertension and underlying lung disease.

Dr Edelman: Yes, I think the context that I brought that up was with the notion of sort of defining patient groups, where the PH was greater than expected.
and I think one of the main reasons to define those groups would be then to say, well, this might be the group that we would study. But I agree, once you sort of pick an enriched population and study it, you’re always left with the question of how broadly applicable the data are to other patient subsets.

Dr Klinger: If we’re looking for a figure that defines these subgroups, you can plot PA pressure on the ordinate and FEV1 or other functions of PFTs on the abscissa and divide patients into four basic quadrants: low PFTs and low PA pressures, low PFTs and high PA pressures, high PFTs and low PA pressures, and then the quadrant that’s up and to the right is those people that have essentially high PFTs, meaning close to normal percentage predicted or mild lung disease and high PA pressures. And that’s where you see most of the mortality—in that mild lung disease, but high PA pressure group. There’s been some suggestion that that’s the group that ought to be focused on.

We did a small trial here years ago, where we simply looked at mortality in our COPD admissions based on their echocardiographic estimates of PA pressure, and found the same trend. High 1 year mortality in COPD patients admitted with acute exacerbation who also have pulmonary hypertension and the group that had the worst survival were those patients who had the highest PA pressures but near normal PFTs.

Dr Schilz: Yeah. It’s also worthwhile, Jim, to extend your data, that also those same patients are ones with COPD that re-exacerbate more frequently, as well.

Dr Klinger: Right.

Dr Schilz: I think we need about 3 more hours of discussion on this. (Laughter) I think few things have been subject to more discussion without concrete resolution than the issues of elevated blood pressures of the lungs in this context of parenchymal lung disease. I do think that perhaps we’re starting to get a more useful structure upon which to base future discussion and, more importantly, investigation.

Dr Edelman: It will be a very thick issue of Advances. But I agree, there’s certainly much more here than could be covered in 45 minutes or 3 hours or even more time. But I also think that among this panel today, we do seem to have fairly good consensus as to when to think about PH in patients with COPD and IPF; how we evaluate these patients; and also on the lack of data for PH-directed therapy and the fact that not only is there a lack of evidence in favor of therapy, but there’s some evidence suggesting that some of the drugs that are used may be harmful as well.

And another important point therefore is to think about when we identify PH in these patient populations, that it may be more of an indicator of prognosis. It may be an indicator for transplant consideration. And it’s certainly an indicator for a diligent search for other associated treatable comorbidities. So making sure we’re aggressive about treating hypoxia, encouraging and assisting with smoking cessation, considering pulmonary rehabilitation, and looking for left heart disease, sleep-disordered breathing, collagen vascular disease and thromboembolic disease.

Dr Schilz: Jeffrey, it is interesting that you bring up the hypoxia part of it. We know that one important treatment in hypoxic COPD patients that has been shown to help is oxygen. But interestingly, that oxygen improved morbidity without changing pulmonary pressures.

Dr Klinger: Yes, but you have to be careful because, the P-value there was 0.07. So it got very, very close to bringing down PA pressure.

Dr Schilz: That study was not designed to look and answer that specific question.

Dr Klinger: Right.

Dr Schilz: It is often important to optimize treatment. But it may be that simply changing the pulmonary pressures may not be all that helpful if it’s just a marker of advanced disease and poor outcome.

Dr Klinger: Yes. I agree completely. The other thing we didn’t get a chance to discuss much is this interesting phenomenon of being able to improve oxygenation by using inhaled pulmonary vasodilators. Once upon a time, the idea of continuous inhaled pulmonary vasodilator therapy was just kind of pie in the sky, but with the advent of the inhaled prostacyclins and ongoing trials of inhaled nitric oxide, there are more patients out there who are using these kinds of medications for that indication. It’s hard to tell whether or not we’re actually achieving improvement, but you can’t argue with the fact that your patient’s oxygen saturation will go from the 80s, or I even have a patient in the 70s now, back to the 90s following their inhaled prostacyclin. It doesn’t last very long, but it allows them to get up and walk around and do their chores and whatnot. We should probably consider discussing when those types of therapies are most appropriate and which patients might potentially benefit from them.

Dr Edelman: I think we’re somewhat time limited there. But are you perhaps suggesting again that this might be a good focus for a clinical trial going forward, as well? Because we’re looking at manifestations of short-term improvement, without really knowing what the long-term impact of those inhaled therapies might be in this patient group.

Dr Klinger: Yes, absolutely.

Dr Schilz: Perhaps again with a different target, of augmenting oxygenation, rather than changing pulmonary pressures, per se.

Dr Klinger: Right.

Dr Edelman: Well, does anyone else have any other closing or summary remarks? If not, I think I will conclude by thanking everyone for participating in this very interesting discussion for what
really amounts to be a fairly common problem in a large population of patients.

**Dr Klinger:** Jeff, I did have just one last thing to add, kind of an overall perspective. I think group 3 PH is really different from the other types of pulmonary hypertension and associated diseases. We have tried for so long to really beat the bushes for early diagnosis and, finding patients who have Group 1 pulmonary hypertension, to get them on treatment. And now, in a sense, we’ve kind of created a huge interest in people that have pulmonary hypertension of other etiologies. I know the practitioners, particularly the modern-day pulmonologists and cardiologists who have made a practice seeing patients with pulmonary hypertensive diseases, are under a lot of pressure with referrals, trying to do something to help these people. But group 3 PH is an area where rather than saying, “Make sure you don’t miss a case of pulmonary hypertension that could have been treated with a pulmonary vasodilator,” we’re really kind of saying, I think collectively, “Be careful who it is that you choose for treatment. And it’s really okay to see somebody and put them through a lot of diagnostic tests and admit that they have pulmonary hypertension associated with their lung disease, but in this particular case, it’s better not to do something for them.” That’s a different approach that we’ve had toward treating pulmonary hypertensive diseases than we’ve had with some of the other PH groups.

**Dr Edelman:** And it also points to the way we, as physicians, are sometimes wired in that we tend to think of diseases as conditions for which we always need to offer treatment. And so we then also need to step back and say, “Well, this condition is present and maybe I don’t have a treatment.” That’s sometimes a very tough position to be in as a physician. It’s often harder to offer no treatment than it is to offer treatment, particularly in the context of a patient/physician interaction.

**Dr Schilz:** Jeffrey, that’s exactly true. Occasionally the most difficult but best thing to do may be not treating PH directly in many Group 3 patients—at least according to the data we have to date.

**Dr Edelman:** I agree and again I want to thank everyone for their participation and input in our discussion of this fascinating and challenging group of patients.
Many caregivers are regularly challenged with questions regarding portable oxygen. There are more options available than ever and one would assume that would simplify things. However, there is more mainstream marketing directed at patients, and some systems are simply not sufficient for patients’ needs.

LOOKING BACK
Forty years ago the only existing “home oxygen” option available was when an industrial supplier of medical gases would deliver a series of “H” cylinders (with brass regulators) to a patient’s home. Times have changed. Today’s choices include home oxygen concentrators, portable oxygen concentrators (POCs), aluminum portable (lighter and smaller) tanks, oxygen conserver (demand) devices, portable liquid oxygen (LOX), and “self-fill” home systems. In this article, we will briefly discuss some of the newer systems and how they work.

DEMAND AND PULSE OXYGEN CONSERVER
While conservers were initially introduced as a way for portable oxygen tanks to last longer, manufacturers have added this technology to some liquid delivery systems and portable concentrators, as well. The basic operating systems of these conservers are either electric or pneumatic.

Electric conservers can operate on an intermittent-breath or every-breath basis. The “smart” technology senses the negative pressure generated at the beginning of inhalation. With an “every-breath” conserver, the solenoid of the conserver opens every time the sensor signals. The length of time it remains open depends on the pulse setting. The higher the pulse setting, the longer the solenoid remains open, thereby increasing the flow. The volume of the pulse is based on the number on the dial, which manufacturers compare to liters per minute (lpm), but it is actually not delivering lpm when in pulse mode. Instead, it is delivering milliliters per breath.

The intermittent-breath conserver senses the breath initiation and fires based on its setting. If the device is set at number 1, it will deliver 1 pulse of a fixed volume of oxygen for every 4 breaths sensed; number 2 will deliver a pulse of oxygen every other breath; number 3 would deliver a pulse of oxygen on 3 out of 4 sensed breaths; and number 4 would deliver it every breath.

A pneumatic conserver senses the initial negative pressure then delivers a fixed pulse of oxygen followed by continuous flow until it senses the beginning of exhalation. For that reason, some pneumatic conservers have a dual cannula (one is attached to the “sensing” port and the other to the “oxygen” port).

Oxygen suppliers stock a variety of systems and it would be very difficult to keep up with the newest developments. When a patient inquires about the eligibility of a conserving device (or a smaller tank), one option is to write a prescription to “titrate and evaluate a patient for a conserving device.” The oxygen company would then assess the patient with the conserver that they supply. After documentation is received identifying the patient’s precise oxygen saturations on that device, the conserver prescription can be approved or denied.

A recurrent challenge with “pulse” dosing is that a patient (when short of breath) will sometimes breathe through their mouth to “catch up.” While “mouth breathing,” the sensor does not always recognize the inspiration and therefore will not fire. Lack of oxygen flow further decreases a patient’s oxygen level and increases shortness of breath (thereby perpetuating the problem). The same may be true at night when a patient does not generate sufficient pressure to trigger the demand device. Each conserver has specific pros and cons. Instructing the home oxygen company to test the patient on the actual conserver provided is the safest option.

CONSERVER TECHNOLOGY HAS BEEN INTEGRATED WITH VARIOUS CURRENT OXYGEN OPTIONS

Liquid Oxygen
Liquid oxygen (LOX) is one of the only viable home oxygen options for patients on liter flows greater than 10 lpm. There are several variations of setups for high-flow patients. Some patients utilize a concentrator for their home and LOX for portability. If a patient requires a flow between 10 and 15 lpm, patients can receive their home flow from a flow-meter attached to a liquid reservoir. The major drawback to LOX is cost and storage of the refill reservoirs. Each standard home reservoir holds about 20 liters of LOX and weighs between 100 and 160 pounds. Smaller reservoirs hold 10 liters and are usually less than 60 pounds (full). The smaller units are the perfect size for travel and can easily

Correspondence: zeiger.tonya@mayo.edu
Table. Personal Oxygen Concentrators

<table>
<thead>
<tr>
<th>Feature</th>
<th>DeVilbiss iGo</th>
<th>Invacare SOLO2</th>
<th>OxLife Independence</th>
<th>Respironics SimplyGo</th>
<th>SeQual Eclipse 2</th>
<th>SeQual SAROS</th>
<th>Airsep Freestyle</th>
<th>Airsep Freestyle 5</th>
<th>Airsep Focus</th>
<th>Airsep Lifestyle</th>
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<tbody>
<tr>
<td>Continuous settings</td>
<td>1.0 to 3.0 LPM</td>
<td>.5 to 3.0 LPM</td>
<td>1 to 3 LPM</td>
<td>0.5, 1, 1.5, 2 LPM</td>
<td>.5 to 3.0 LPM</td>
<td>1, 2 &amp; 3 lpm</td>
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<td>.5 LPM</td>
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<td>.5 LPM</td>
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<td>Battery life</td>
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<td>1.1 hrs</td>
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<td>Average delivery</td>
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<td>Battery life</td>
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<td></td>
<td>1.8 hours</td>
<td>45 min</td>
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<td>Maximum delivery</td>
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<td>3.0 LPM</td>
<td>3 LPM</td>
<td>2 lpm</td>
<td>3 LPM</td>
<td>3 lpm</td>
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<td>.9 hours</td>
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<td>30 minutes</td>
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<td>Pulse settings</td>
<td>1.0 to 6.0</td>
<td>1 to 5</td>
<td>1 to 6</td>
<td>.5 to 6.0 (0.5 increments)</td>
<td>16, 32, 48, 64, 80, 96 ml</td>
<td>1 to 3</td>
<td>1 to 5</td>
<td>A single pulse setting (equiv of 2LPM)</td>
<td>1 to 5</td>
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<td>setting 1</td>
<td>16 ml</td>
<td>setting 1</td>
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<td>Oxygen delivery output</td>
<td>16 ml</td>
<td>16 ml</td>
<td>16 ml</td>
<td>12 ml</td>
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<td>setting 2</td>
<td>48 ml</td>
<td>setting 2</td>
<td>setting 3</td>
<td>setting 2</td>
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<td>Oxygen delivery output</td>
<td>32 ml</td>
<td>32 ml</td>
<td>32 ml</td>
<td>24 ml</td>
<td>32 ml</td>
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<td>Battery life</td>
<td>4.8 hours</td>
<td>3.5 hours</td>
<td>3 hours</td>
<td>3 hrs</td>
<td>53 min</td>
<td>2.5 hours</td>
<td>1.5 hours-up to 3.3 hours with optional Air Belt</td>
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<td></td>
<td></td>
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<tr>
<td>Maximum delivery at</td>
<td>setting 6</td>
<td>setting 6</td>
<td>setting 6</td>
<td>setting 6</td>
<td>96 ml</td>
<td>setting 3</td>
<td>setting 5</td>
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<tr>
<td>Oxygen delivery output</td>
<td>96 ml</td>
<td>80 ml</td>
<td>96 ml</td>
<td>72 ml</td>
<td>96 ml</td>
<td>43.75ml +/- 10%</td>
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<td>Weight</td>
<td>15.5 pounds</td>
<td>17 pounds</td>
<td>11.85 pounds</td>
<td>10 lbs w/battery</td>
<td>14.5 lbs</td>
<td>10.0 lbs</td>
<td>4.4 pounds</td>
<td>5.8 lbs</td>
<td>9.75 pounds</td>
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<tr>
<td>1 battery</td>
<td>19 pounds</td>
<td>19.9 pounds</td>
<td>14.85 pounds</td>
<td>18 pounds</td>
<td>12.25 lbs /w battery</td>
<td>5.8 pounds</td>
<td>add .53 lb / battery</td>
<td>1.75lb + .53lb per battery</td>
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<tr>
<td>1 battery &amp; shoulder bag</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td>1.8 lb AirBelt (opt)</td>
<td>1.8 lb AirBelt (opt)</td>
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<td>1 battery &amp; cart</td>
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<tr>
<td>2 battery &amp; shoulder bag</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>1.8 lb AirBelt (opt)</td>
<td>1.8 lb AirBelt (opt)</td>
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<tr>
<td>Size (Height X Width X Depth)</td>
<td>15H-11W-8D</td>
<td>16.55H-11W-8D</td>
<td>12H-8W-8D</td>
<td>11.5H-10W-6D</td>
<td>18H-12.3W-7.1D</td>
<td>26.80H-4.375 dia</td>
<td>8.6H-6.1W-3.6D</td>
<td>10.5H-6.4W-4.4D</td>
<td>6.4H-4.8W-2.5D</td>
<td>5.5H-7.25W-6.31D</td>
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<tr>
<td>Sound level</td>
<td>38-40 dBA</td>
<td>35-42 dBA</td>
<td>41-44 dBA</td>
<td>43 dB @ setting 2</td>
<td>40 dB @ 3.0 pulse-48dB @ 3.0 Lp continuous</td>
<td>&lt;59 dB</td>
<td>38-44 dBA</td>
<td>41 dBA at setting 2</td>
<td>50 dBA</td>
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<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Maximum altitude (see note #1)</td>
<td>13,123 ft</td>
<td>10,000 ft</td>
<td>10,000 ft</td>
<td>13,123 ft</td>
<td>18,000 ft</td>
<td>12,000 ft</td>
<td>12,000 ft</td>
<td>10,000 ft</td>
<td>12,000 ft</td>
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<tr>
<td>Oxygen concentration</td>
<td>91% ± 3%</td>
<td>87-95.6%</td>
<td>90% + 3%</td>
<td>86% to 97%</td>
<td>90% ± 3%</td>
<td>93% + 3%</td>
<td>90% ± 3%</td>
<td>90% + 3.5%-3%</td>
<td>90%+ .5/-3%</td>
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</tr>
<tr>
<td>Oxygen output pressure</td>
<td>12.0 psig</td>
<td>4 psi</td>
<td>3 psi</td>
<td>5.0 psig</td>
<td>4.0 psig</td>
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<tr>
<td>Max. Hose length (see note #3)</td>
<td>35P 50 C</td>
<td>7 P 25C</td>
<td>30 ft</td>
<td>7 P 50C</td>
<td>7 ft</td>
<td></td>
<td></td>
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<tr>
<td>Maximum oxygen capacity</td>
<td>3,000 ml / min</td>
<td>3,000 ml / minute</td>
<td>2000 ml/min</td>
<td>3,000 ml / minute</td>
<td></td>
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<tr>
<td>Maximum Breaths/minute</td>
<td>35</td>
<td>30</td>
<td>40</td>
<td>31 to 40 (96-16 p)</td>
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<tr>
<td></td>
<td>Inogen One</td>
<td>Inogen One G2</td>
<td>Inogen One G3</td>
<td>International Biophysics Corporation LifeChoice</td>
<td>Invacare XPO2</td>
<td>Inova Labs LifeChoice Activox</td>
<td>Oxus RS00-400 / Delphi RS00-400</td>
<td>Respironics EverGo</td>
<td>Precision Medical Easy Pulse</td>
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<tr>
<td><strong>Continuous settings</strong></td>
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<tr>
<td>Minimum delivery</td>
<td>1 to 5 plus a “satellite” setting</td>
<td>1 to 5 plus a “satellite” setting</td>
<td>1 to 4</td>
<td>1 to 3</td>
<td>1 to 5</td>
<td>1 to 3</td>
<td>1 to 5</td>
<td>1 to 5</td>
<td>1 to 6</td>
<td>1 to 5</td>
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<td>Battery life</td>
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<td><strong>Battery life</strong></td>
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<td></td>
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</tr>
<tr>
<td>Minimum delivery at</td>
<td>setting 1</td>
<td>setting 1</td>
<td>setting 1 @ 20 bpm</td>
<td>setting 1</td>
<td>setting 1</td>
<td>setting 1</td>
<td>setting 1</td>
<td>setting 1</td>
<td>setting 1</td>
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<tr>
<td>Battery life</td>
<td>3 hours</td>
<td>4 hours on single battery - 8 hrs on double battery</td>
<td>up to 4.5 hrs single battery - up to 9 hrs double battery</td>
<td>2+ hours on Internal battery on all settings (add 3 hrs with battery)</td>
<td>3 hours</td>
<td>12 hrs /w internal battery add 3 hrs for external battery</td>
<td>5 hours per battery</td>
<td>4.5 hrs</td>
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<tr>
<td>Average delivery at</td>
<td>setting 2</td>
<td>setting 2</td>
<td>setting 2 @ 20 bpm</td>
<td>setting 2</td>
<td>setting 2</td>
<td>setting 2</td>
<td>setting 2</td>
<td>setting 2</td>
<td>setting 3</td>
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<tr>
<td>Battery life</td>
<td>2.5 hours</td>
<td>2.5 hours</td>
<td>18.0 ml +/- 10%</td>
<td>2.5 hours</td>
<td>6 hrs (internal battery) +3 hrs for external battery</td>
<td>3 hours at 15 BPM</td>
<td>2.5 hrs</td>
<td>4 hours-per battery</td>
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<td>Maximum delivery at</td>
<td>setting 6</td>
<td>setting 6</td>
<td>setting 4 @ 20 bpm</td>
<td>setting 3</td>
<td>setting 5</td>
<td>setting 3</td>
<td>setting 6</td>
<td>setting 5</td>
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<tr>
<td>Battery life</td>
<td>1 hours</td>
<td>1 hours</td>
<td>18.0 ml +/- 10%</td>
<td>1 hours</td>
<td>5 hrs (internal battery) +2 hrs for external battery</td>
<td>2 hours-per battery</td>
<td>1.5 hrs</td>
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<td>Weight</td>
<td>4.8 lbs with 1 battery</td>
<td>4.9 lbs</td>
<td>4.83 lbs</td>
<td>9.8 pounds</td>
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<tr>
<td>1 battery</td>
<td>7 lbs.</td>
<td>add 1 lb for external battery</td>
<td>6 pounds</td>
<td>8.5 pounds</td>
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<tr>
<td>1 battery &amp; shoulder bag</td>
<td>12 pounds</td>
<td>12 pounds</td>
<td>6 pounds</td>
<td>10 pounds</td>
<td>12 pounds</td>
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<td>2 battery &amp; shoulder bag</td>
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<td>10 pounds</td>
<td>13 pounds</td>
<td>9.9 pounds</td>
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<tr>
<td><strong>Size (Height X Width X Depth)</strong></td>
<td>12.4H-11.6W-6D</td>
<td>9.5H-10.7W-3.9D</td>
<td>2.5H-8.75W-3.0D</td>
<td>9H-7W-4D</td>
<td>10H-7W-4D</td>
<td>7.875H-9.5W-4.38D</td>
<td>7.4W-4.6-11.6H</td>
<td>8.5H-12W-6D</td>
<td>10.1H-6.5W-4.5D</td>
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<td>Sound level</td>
<td>37-40 dBA</td>
<td>38 dBA</td>
<td>42 dBA at setting 2</td>
<td>&lt; 50 dBA</td>
<td>44-46 dBA</td>
<td>41 dB at setting 1</td>
<td>46 dB at setting 3</td>
<td>42-44 dBA</td>
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<td>FAA Approval</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Maximum altitude (note #1)</td>
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<td>10,000 ft</td>
<td>10,000 ft</td>
<td>10,000 ft</td>
<td>10,000 ft</td>
<td>10,000 ft</td>
<td>10,000 ft</td>
<td>8,000 ft</td>
<td>9,000 ft</td>
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<tr>
<td>Oxygen concentration</td>
<td>90% ± 3%</td>
<td>90%-3%; +6%</td>
<td>90%-3%; +6%</td>
<td>90% ± 3%</td>
<td>90% ± 3%</td>
<td>90% (± 3%)</td>
<td>90% ± 3%</td>
<td>90% ± 3%</td>
<td>90% ± 3%</td>
<td></td>
</tr>
<tr>
<td>Oxygen output pressure</td>
<td>3 psi</td>
<td>3 psi</td>
<td>3 psi</td>
<td>3 psi</td>
<td>3 psi</td>
<td>3 psi</td>
<td>3 psi</td>
<td>3 psi</td>
<td>3 psi</td>
<td></td>
</tr>
<tr>
<td>Max. Hose length (note #3)</td>
<td>25 ft (w/ high flow)</td>
<td>9 ft</td>
<td>9 ft</td>
<td>25 ft (w/ high flow)</td>
<td>9 ft</td>
<td>9 ft</td>
<td>25 ft (w/ high flow)</td>
<td>9 ft</td>
<td>9 ft</td>
<td></td>
</tr>
<tr>
<td>Maximum oxygen capacity</td>
<td>750 ml/minute</td>
<td>900 ml/minute</td>
<td>900 ml/minute</td>
<td>925 ml/minute sustained- 1200ml for short periods</td>
<td>1050 ml/minute</td>
<td>925 ml/minute sustained- 1200ml for short periods</td>
<td>1050 ml/minute</td>
<td>925 ml/minute sustained- 1200ml for short periods</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum Breaths /minute</td>
<td>30</td>
<td>35</td>
<td>35</td>
<td>35</td>
<td>35</td>
<td>35</td>
<td>35</td>
<td>35</td>
<td>35</td>
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</tbody>
</table>
be transported in mid- to large-sized automobiles (as long as the home oxygen company will allow it). How often the oxygen company refills the patient’s reservoir depends on liter flow and the rate of evaporation. Consider LOX if your patient requires high flows.

**Self-Fill Systems**
In recent years reimbursement for home oxygen has decreased, and it has become more fiscally challenging for oxygen companies. With home oxygen companies trying to find more ways to deliver care with fewer deliveries and less upkeep, a new product was developed in 2000, enabling home oxygen patients to fill their own portable gas cylinders from their oxygen concentrator. The key with this system is that a cylinder filled with a concentrator will not contain 100% oxygen. A properly functioning concentrator can produce an oxygen concentration as low as 88%; therefore, that would be the percentage of oxygen filling the patient’s portable tank. While there have been studies citing this as clinically inconsequential, it should be noted, particularly if your patient needs liter flows >4 lpm.

**Portable Oxygen Concentrator**
The newest addition to the oxygen world is the POC. There are several factors to consider with each option, keeping in mind all of the particulars discussed previously. Since the 2005 landmark decision by the Federal Aviation Administration to allow POCs on commercial aircraft, there have been a host of new POCs introduced. While 5 portable concentrators have the ability to provide continuous flow and they are limited to a maximum of 3 lpm, the majority of POCs deliver oxygen by pulse flow only. Considerations for selection of a POC include: weight, size, battery life, maximum oxygen capacity, sound level, and oxygen hose length. POC weights with a single battery range from 2.3 to 19.9 pounds. In general, lighter units have shorter battery life and lower maximum oxygen capacities. Battery life varies by POC unit and flow rate used, ranging from <1 hour to 6 hours. Utilizing extra batteries can extend the time between charges. The more details we learn about how portable concentrators work, the more we can appropriately gauge which patients may benefit most from this technology. Different options are constantly emerging.

When initiating oxygen therapy, it is wise to discuss the patient’s expectations and lifestyle. Some patients have frequent travel plans and should select a company that can and will accommodate those needs. The world of oxygen systems is ever changing and new developments must be addressed. The focus should center on developing individualized patient oxygen therapy plans as new options emerge.

An important tool in the arena of patient self-monitoring is the portable pulse oximeter. In recent years, the portable pulse oximeter has become increasingly affordable. While it is not a perfect tool, a home pulse oximeter can be very helpful for a patient to report their oxygenation while in the home setting. This is especially true in monitoring patients with exercise-related dyspnea and for titrating oxygen flow for patients on long-term oxygen therapy, provided their disease is stable and they have good circulation. In general, the goal should be to maintain oxygen saturation >90% during all activities.

Pulse oximeters can overestimate oxygen saturation, particularly in those with darkly pigmented skin. Additional cautions should be noted if the patient has:
- Poor perfusion due to systemic hypotension, Raynaud’s, hypovolemic shock, cold environment, or cardiac failure— it may result in the machine not providing a reading (or an inaccurate reading)
- Anemia—oxygen delivery to tissues is inadequate due to lack of hemoglobin for oxygen to bind to, but oxygen saturation is normal
- Carbon monoxide poisoning—carbon monoxide binds to hemoglobin, resulting in inadequate oxygen transport despite normal pulse oximeter readings. The pulse oximeter cannot distinguish what gas is binding to the hemoglobin (only that a gas is attached).
- Movement, shivering patient, heart arrhythmias—oximeter may not be able to identify an adequate pulse signal due to movement intolerance
- Nail polish, dirt, artificial nails—can cause false low readings or prevent readings altogether

It is difficult to predict whether a patient will be appropriately oxygenated with a particular system, but by working closely with patients and home oxygen providers, patients can truly live life to its fullest.

**References**
IMPORTANT SAFETY INFORMATION

ADD MORE to your treatment strategy

+ PAH may be progressing even if patients seem stable
+ Many patients plateau on oral therapy (PDE-5 inhibitor or ERA) within 12 weeks

ADD MORE: Tyvaso is the only PAH treatment approved as an add-on to oral therapy

+ After 1.7 years (mean) on oral monotherapy, adding Tyvaso for 12 weeks improved median 6MWD by 20 m (P<0.001)
+ 4X daily dosing with short treatment sessions (2-3 minutes) approximately every 4 hours

Study design: TRIUMPH I was a 12-week, randomized, double-blind, placebo-controlled, multicenter study of patients (N=295) with PAH who were receiving a stable dose of bosentan or sildenafil for 3 months before study initiation. Patients were administered either placebo or Tyvaso in 4 daily treatment sessions with a target dose of 9 breaths (54 mcg) per session over the course of the 12-week study. Primary endpoint was change in 6MWD at 12 weeks. Secondary endpoints included time to clinical worsening, Borg dyspnea score, NYHA functional class, trough 6MWD at week 12 (obtained at least 4 hours after study drug administration), peak 6MWD at 6 weeks, quality of life as measured by the MLWHF questionnaire, and PAH signs and symptoms.

INDICATION

Tyvaso is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominantly patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%). The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities.

While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor). The controlled clinical experience was limited to 12 weeks in duration.

IMPORTANT SAFETY INFORMATION

Tyvaso is intended for oral inhalation only. Tyvaso is approved for use only with the Tyvaso Inhalation System.

+ The safety and efficacy of Tyvaso have not been established in patients with significant underlying lung disease (such as asthma or chronic obstructive pulmonary disease) and in patients under 18 years of age. Patients with acute pulmonary infections should be carefully monitored to detect any worsening of lung disease and loss of drug effect.
+ Tyvaso may increase the risk of bleeding, particularly in patients receiving anticoagulants.
+ In patients with low systemic arterial pressure, Tyvaso may cause symptomatic hypotension. The concomitant use of Tyvaso with diuretics, antihypertensives, or other vasodilators may increase the risk of symptomatic hypotension.
+ Hepatic or renal insufficiency may increase exposure to Tyvaso and decrease tolerability. Tyvaso dosage adjustments may be necessary if inhibitors of CYP2C8 such as gemfibrozil or inducers such as rifampin are added or withdrawn.

ADD MORE: Tyvaso is the only PAH treatment approved as an add-on to oral therapy

+ The most common adverse events seen with Tyvaso in ≥4% of PAH patients and more than 3% greater than placebo in the placebo-controlled clinical study were cough (54% vs 29%), headache (41% vs 23%), throat irritation/pharyngolaryngeal pain (25% vs 14%), nausea (19% vs 11%), flushing (15% vs <1%), and syncope (6% vs <1%).
+ Tyvaso should be used in pregnancy only if clearly needed. Caution should be exercised when Tyvaso is administered to nursing women.

Please see brief summary of Full Prescribing Information on following page. For more information, please see Full Prescribing Information, Patient Package Insert, and the Tyvaso Inhalation System Instructions for Use manual. These items are available at www.tyvaso.com.

6MWD=6-minute walk distance. MLWHF=Minnesota Living With Heart Failure. NYHA=New York Heart Association. PAH=pulmonary arterial hypertension. WHO=World Health Organization.

References:
The safety of TYVASO was also studied in a long-term, open-label extension study in which 206 patients were dosed for a mean duration of one year. The adverse events during this chronic dosing study were qualitatively similar to those observed in the 12-week placebo controlled trial. Adverse Events Associated with Route of Administration–Adverse events in the treated group during the double-blind and open-label phase reflecting irritation to the respiratory tract included: cough, throat irritation, pharyngolaryngeal pain, epistaxis, hemoptysis and wheezing. Serious adverse events during the open-label portion of the study included pneumonia in 8 subjects. There were three serious episodes of hemoptysis (one fatal) noted during the open-label experience.

**DRUG INTERACTIONS**
Pharmacokinetic/pharmacodynamic interaction studies have not been conducted with inhaled treprostinil (TYVASO); however, some of such studies have been conducted with orally (treprostinil diethanolamine) and subcutaneously administered treprostinil (Remodulin®).

- Pharmacodynamics—Antiplatelet Agents or Other Vasodilators–Concomitant administration of TYVASO with diuretics, antiplatelet agents or other vasodilators may increase the risk of symptomatic hypotension. Anticoagulants—Since treprostinil inhibits platelet aggregation, there may be an increased risk of bleeding, particularly among patients receiving antiplatelet therapy.
- Effect of Other Drugs on Treprostinil–Co-administration of a cytochrome P450 (CYP) 2C8 enzyme inhibitor (e.g., gemfibrozil) may increase exposure (both Cmax and AUC) to treprostinil. Co-administration of a CYP2C8 enzyme inducer (e.g., rifampin) may decrease exposure to treprostinil. Increased exposure is likely to increase adverse events associated with treprostinil administration, whereas decreased exposure is likely to reduce clinical effectiveness.

**ADVERSE REACTIONS**
The following potential adverse reactions are described in Warnings and Precautions:

- Decrease in systemic blood pressure
- Bleeding

Adverse Reactions Identified in Clinical Trials—Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In a 12-week placebo-controlled study (TRIUMPH I) of 235 patients with PAH (WHO Group I and nearly all NYHA Functional Class III), the most commonly reported adverse reactions to TYVASO included: cough and throat irritation; headache; gastrointestinal effects; muscle, jaw or bone pain; flushing and syncope. Table 1 lists the adverse reactions that occurred at a rate of at least 4% and were more frequent in patients treated with TYVASO than with placebo.

Table 1: Adverse Events in ≥4% of PAH Patients Receiving TYVASO and More Frequent* than Placebo

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>TYVASO n (%)</th>
<th>Placebo n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>62 (54)</td>
<td>35 (29)</td>
</tr>
<tr>
<td>Headache</td>
<td>47 (41)</td>
<td>27 (23)</td>
</tr>
<tr>
<td>Throat Irritation/Pharyngolaryngeal Pain</td>
<td>29 (25)</td>
<td>17 (14)</td>
</tr>
<tr>
<td>Nausea</td>
<td>22 (19)</td>
<td>13 (11)</td>
</tr>
<tr>
<td>Flushing</td>
<td>17 (15)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Syncope</td>
<td>7 (6)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

*More than 3% greater than placebo

Pregnancy—Pregnancy Category B–There are no adequate and well controlled studies with TYVASO in pregnant women. Animal reproduction studies have not been conducted with treprostinil administered by the inhalation route. However, studies in pregnant rabbits using continuous subcutaneous (sc) infusions of treprostinil sodium at infusion rates higher than the recommended human sc infusion rate resulted in an increased incidence of fetal skeletal variations associated with maternal toxicity. Animal reproduction studies are not always predictive of human response; TYVASO should be used during pregnancy only if clearly needed.

Labor and Delivery–No treprostinil treatment-related effects on labor and delivery were seen in animal studies. The effect of treprostinol on labor and delivery in humans is unknown.

Nursing Mothers–It is not known whether treprostinil is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when treprostinil is administered to nursing women.

Pediatric Use–Safety and effectiveness in pediatric patients have not been established. Clinical studies of TYVASO did not include patients younger than 18 years to determine whether they respond differently from older patients.

Genetic Use–Clinical studies of TYVASO did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of hepatic, renal, or cardiac dysfunction, and of concomitant diseases or other drug therapy.

Patients with Hepatic Insufficiency–Plasma clearance of treprostinil, delivered subcutaneously, was reduced up to 80% in subjects with mild-to-moderate hepatic insufficiency. Uptitrate slowly when treating patients with hepatic insufficiency because of the risk of an increase in systemic exposure which may lead to an increase in dose-dependent adverse effects. Treprostinil has not been studied in patients with severe hepatic insufficiency.

Patients with Renal Insufficiency–No studies have been performed in patients with renal insufficiency. Since treprostinil and its metabolites are excreted mainly through the urinary route, patients with renal insufficiency may have decreased clearance of the drug and its metabolites and consequently, dose-related adverse outcomes may be more frequent.

**OVERDOSAGE**
In general, symptoms of overdose with TYVASO include flushing, headache, hypotension, nausea, vomiting, and diarrhea. Provide general supportive care until the symptoms of overdose have resolved.

**CONTRAINDICATIONS**
None.

**WARNINGS AND PRECAUTIONS**
Patients with Pulmonary Disease or Pulmonary Infections–The safety and efficacy of TYVASO have not been established in patients with significant underlying lung disease (e.g., asthma or chronic obstructive pulmonary disease). Patients with acute pulmonary infections should be carefully monitored to detect any worsening of lung disease and loss of drug effect.

Risk of Symptomatic Hypotension–Treprostinil is a pulmonary and systemic vasodilator. In patients with low systemic arterial pressure, treatment with TYVASO may produce symptomatic hypotension.

Patients with Hepatic or Renal Insufficiency–Titrate slowly in patients with normal hepatic or renal function. Increased exposure is likely to increase adverse events associated with treprostinil administration, whereas decreased exposure is likely to reduce clinical effectiveness.

Risk of Bleeding–Since TYVASO inhibits platelet aggregation, there may be an increased risk of bleeding, particularly among patients receiving antiplatelet therapy.

Effect of Other Drugs on Treprostinil–Co-administration of a cytochrome P450 (CYP) 2C8 enzyme inhibitor (e.g., gemfibrozil) may increase exposure (both Cmax and AUC) to treprostinil. Co-administration of a CYP2C8 enzyme inducer (e.g., rifampin) may decrease exposure to treprostinil. Increased exposure is likely to increase adverse events associated with treprostinil administration, whereas decreased exposure is likely to reduce clinical effectiveness.
**NEWS TO USE**

**PHA Classroom**

PHA Classroom hosts and archives live e-learning events targeted toward patients and caregivers that cover a wide array of topics to help improve their lives. Recent recordings include:
- Pulmonary Hypertension in Chronic Obstructive Pulmonary Disease
- Surviving Survivor’s Guilt
- Chronic Thromboembolic Pulmonary Hypertension—What You Need to Know
- Exercise-Induced Pulmonary Hypertension—What Is It and What Do We Do About It?

You and your patients can view recent recordings and upcoming live e-learning events at [www.PHAssociation.org/Classroom](http://www.PHAssociation.org/Classroom).

**PHA Resources for Patients**

PHA offers ongoing education and information for patients and caregivers at every stage of their PH journeys. We now provide resources to help your patients and caregivers cope with the mental, emotional and social impacts of living with PH. Order your Coping Guides Postcards to point patients and caregivers to these resources at [www.PHAssociation.org/ForYourPatients](http://www.PHAssociation.org/ForYourPatients).

**PHA Online University**

View new releases of medical education courses on [PHA Online University](http://www.PHAssociation.org/).

Recent additions include:
- **Sickle Cell Disease and PH**
  Roberto Machado, MD, University of Illinois College of Medicine at Chicago, Chicago, IL
  Nov. 2013
  View this course at [www.PHAssociation.org/SickleCellDisease](http://www.PHAssociation.org/SickleCellDisease)
- **PAH in Systemic Lupus Erythematosus**

**Join Team PHenomenal Hope**

UPMC PH-treating pulmonologist, Dr Patty George, and her cycling team, Team PHenomenal Hope, will be competing in the ultra-endurance “Race Across America” cycling race in June 2014 to raise funds in the fight against pulmonary hypertension. Join Dr George and PHA on Saturday, April 14 to cover a PHenomenal Mile wherever you live in solidarity with the team. Lace up your sneakers, get on your bike, and grab your colleagues to support this extraordinary doctor’s efforts. Go the extra mile and donate online to the Race of Our Lives campaign. For more info visit: [http://www.phassociation.org/RaceOfOurLives](http://www.phassociation.org/RaceOfOurLives)

**GUEST EDITOR’S MEMO (continued from page 106)**

patients (perhaps among those with “out of proportion PH”) may have more than one disease process and therefore could potentially benefit from PH directed treatment.

Success in our present understanding of Group 1 PAH rests on foundations of basic science, prospective registries, and focused clinical trials. A reiteration of this approach for Group 3 and other PH groups should be fostered. While reading this issue, consider how to plot a course to advance knowledge in the realm of Group 3 PH.

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VA Puget Sound Health Care System
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**References**

Go to www.letairis.com to learn more.
Letairis® (ambrisentan) 5 mg and 10 mg Tablets, for oral use.

DOSAGE AND ADMINISTRATION: Adult Dosing: Initiate treatment at 5 mg once daily, and consider increasing the dose to 10 mg once daily if 5 mg is well tolerated. Tablets may be administered with or without food.

CONTRAINDICATIONS: Pregnancy: Letairis may cause fetal harm when administered to a pregnant female. Letairis is contraindicated in pregnant females as this effect has been seen consistently when it is administered to animals.

USE IN SPECIFIC POPULATIONS: Pregnancy Category X: Letairis is contraindicated in patients with prior human embryo-fetal toxicity. Letairis is very likely to produce serious birth defects if used by pregnant females, and results in fetal deaths when administered to pregnant animals.

INDICATIONS AND USAGE: Letairis is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise ability and delay clinical worsening. Studies establishing effectiveness included predominantly patients with WHO Functional Class II-III symptoms and etiologies of idiopathic or heritable PAH (64%) or PAH associated with connective tissue disease (32%).

INDICATIONS AND USAGE: Letairis is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise ability and delay clinical worsening. Studies establishing effectiveness included predominantly patients with WHO Functional Class II-III symptoms and etiologies of idiopathic or heritable PAH (64%) or PAH associated with connective tissue disease (32%).

Fluid Retention: Pharmacies that dispense Letairis must be certified with the program and dispense to female patients who are authorized to receive Letairis. Further information is available at [Use in Specific Populations].

Nonclinical Toxicology

Hematological Changes: Decreased Sperm Counts: Decreased sperm counts have been observed in human and animal studies with another endothelin receptor antagonist and in animal fertility studies with Letairis. Letairis may have an adverse effect on spermatogenesis. Counsel patients about potential effects on fertility [see Special Populations].

Hematological Changes: Decreases in hemoglobin concentration and hematocrit have followed administration of other endothelin receptor antagonists and were observed in clinical studies with Letairis. These decreases were observed within the first few weeks of treatment with Letairis, and stabilized thereafter. The mean decrease in hemoglobin from baseline to end of treatment was approximately 0.8 g/dL in patients treated with Letairis. Patients receiving placebo controlled studies was 0.9 g/dL. Marked decreases in hemoglobin (>50% decrease from baseline resulting in a value below the lower limit of normal) were observed in 7% of all patients receiving Letairis (and 10% of patients receiving placebo). The cause of the decrease in hemoglobin was unknown, but it does not appear to result from hemorrhage or hemolysis. In the long-term open-label extension of the two pivotal clinical studies, mean decreases from baseline (ranging from 0.9 to 1.2 g/dL) in hemoglobin concentrations persisted for up to 4 years of treatment. There have been postmarketing reports of decreases in hemoglobin concentrations: ALT elevations <5 x ULN, but 9 patients had elevations >5 x ULN. Eight patients had been re-challenged with bosentan and/or the investigational ERA and all eight had a recurrence of amino transferase abnormalities that required discontinuation of ERA therapy. All patients had to have normal amino transferase levels on entry to this study. Twenty-five of the 36 patients were also receiving prostanoids and/or phosphodiesterase type 5 (PDE5) inhibiting therapy. Two patients discontinued early (including one of the patients with a prior >5 x ULN elevation).

Drugs, Herbs, and Other Substances

Fluid Retention: Peripheral edema is a known class effect of endothelin receptor antagonists, and is also a clinical consequence of PAH and worsening PAH. In the placebo controlled studies, there was an increased incidence of peripheral edema in patients treated with doses of 5 or 10 mg Letairis compared to placebo [see Warnings and Precautions].

Most adverse drug reactions were mild to moderate and only nasal congestion was dose dependent. Most adverse reactions were observed within the first 3 months of treatment [see Adverse Reactions].

Flushing: Peripheral edema was similar in younger patients (<65 years) receiving Letairis (14% of patients) and placebo (13% of patients) vs elderly patients (10% of patients) who were treated with Letairis (29%) and placebo (16%) in the perioperative period. Peripheral edema was also reported in patients who had undergone both surgical and medical treatment with Letairis. Adequate adverse reactions to the occurrence of >5% more patients receiving Letairis than receiving placebo are shown in Table 1.

Table 1: Adverse Reactions with Placebo-Adjusted Rates >3%

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Placebo (n=132)</th>
<th>Letairis (n=261)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral edema</td>
<td>14 (11)</td>
<td>45 (17)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>1 (1)</td>
<td>15 (6)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>0 (0)</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Flushing</td>
<td>1 (1)</td>
<td>11 (4)</td>
</tr>
</tbody>
</table>

The mean decrease in hemoglobin from baseline to end of treatment for those patients receiving Letairis in the 12 week placebo controlled studies was 0.8 g/dL. During 12-week placebo-controlled studies, 36 patients experienced asymptomatic elevations of serum aminotransferase enzymes (>2 x upper limit of normal) and of these, 9% were observed in patients who had experienced asymptomatic amino transferase elevations on other ERAs after amino transferase levels have returned to normal. Postmarketing Experience: The following adverse reactions were identified during postapproval use of Letairis. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to estimate reliably the frequency or to establish a causal relationship to drug exposure: nausea and vomiting, fluid retention [see Warnings and Precautions], and increased serum liver enzymes [see Clinical Pharmacology].

USE IN SPECIFIC POPULATIONS: Pregnancy Category X: Letairis is contraindicated in patients with prior human embryo-fetal toxicity. Letairis is very likely to produce serious birth defects if used by pregnant females, and results in fetal deaths when administered to pregnant animals.

Drug Interactions: Letairis should not be administered to a pregnant woman and is contraindicated during pregnancy. Letairis was teratogenic in rats and rabbits at doses which resulted in exposures of 3.5 and 1.7 times respectively the human dose of 10 mg per day. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential hazard to a fetus [see Contraindications, Warnings and Precautions].

Females and Males of Reproductive Potential: Use of Letairis in pregnant females who have experienced asymptomatic amino transferase elevations on other ERAs after amino transferase levels have returned to normal. Postmarketing Experience: The following adverse reactions were identified during postapproval use of Letairis. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to estimate reliably the frequency or to establish a causal relationship to drug exposure: nausea and vomiting, fluid retention [see Warnings and Precautions], and increased serum liver enzymes [see Clinical Pharmacology].

Use in Specific Populations: Pregnancy Category X: Letairis is contraindicated in patients with prior human embryo-fetal toxicity. Letairis is very likely to produce serious birth defects if used by pregnant females, and results in fetal deaths when administered to pregnant animals.

Drug Interactions: Multiple dose co-administration of ambrisentan and cyclosporine resulted in an approximately 2-fold increase in ambrisentan exposure in healthy volunteers; therefore, limit the dose of ambrisentan to 5 mg once daily when co-administered with cyclosporine [see Clinical Pharmacology].

Use in Specific Populations: Pregnancy Category X: Letairis is contraindicated in patients with prior human embryo-fetal toxicity. Letairis is very likely to produce serious birth defects if used by pregnant females, and results in fetal deaths when administered to pregnant animals.

Drug Interactions: Multiple dose co-administration of ambrisentan and cyclosporine resulted in an approximately 2-fold increase in ambrisentan exposure in healthy volunteers; therefore, limit the dose of ambrisentan to 5 mg once daily when co-administered with cyclosporine [see Clinical Pharmacology].

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Drug Interactions: Multiple dose co-administration of ambrisentan and cyclosporine resulted in an approximately 2-fold increase in ambrisentan exposure in healthy volunteers; therefore, limit the dose of ambrisentan to 5 mg once daily when co-administered with cyclosporine [see Clinical Pharmacology].
Warning and Dosage and Administration

Contraception: Female patients of reproductive potential must use acceptable methods of contraception during treatment with Letairis and for 1 month after stopping treatment with Letairis. Patients may choose one highly effective form of contraception (intrauterine devices, IUD), contraceptive implants, or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a partner's surgery is performed, the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider trained in contraceptive counseling (see Boxed Warning; Infertility). Males In a 6-month study of another endothelin receptor antagonist, bosentan, 25 functional class III and IV PAH and normal baseline sperm count were evaluated for effects on testicular function. There was a decline in sperm count of at least 50% in 25% of the patients after 3 or 6 months of treatment with bosentan. One patient developed marked oligospermia at 3 months and the sperm count remained low with 2 follow-up measurements over the subsequent 6 weeks. Bosentan was discontinued and after 2 months the sperm count had returned to baseline levels. In 22 patients who completed 6 months of treatment, sperm count remained within the normal range and no changes in sperm morphology, sperm motility, or hormone levels were observed. Based on these findings, and preclinical data (see Nonclinical Toxicology) from endothelin receptor antagonists, it cannot be excluded that endothelin receptor antagonists such as Letairis have an adverse effect on spermatogenesis. Counsel patients about the potential effects on fertility (see Warnings and Precautions). Renal Impairment: The impact of renal impairment on the pharmacokinetics of ambrisentan has been examined using a population pharmacokinetic approach in PAH patients with creatinine clearances ranging between 20 and 150 mL/min. There was no significant impact of mild or moderate renal impairment on exposure to ambrisentan (see Clinical Pharmacology). Dose adjustment of Letairis in patients with mild or moderate renal impairment is therefore not required. There is no information on the exposure to ambrisentan in patients with severe renal impairment. The impact of hemodialysis on the disposition of ambrisentan has not been investigated. Hepatic Impairment: Pre-existing hepatic impairment: The influence of pre-existing hepatic impairment on the pharmacokinetics of ambrisentan has not been evaluated. Because there is in vitro and in vivo evidence of significant metabolic and biliary contribution to the elimination of ambrisentan, hepatic impairment would be expected to have significant effects on the pharmacokinetics of ambrisentan (see Clinical Pharmacology). Letairis is not recommended in patients with moderate or severe hepatic impairment. There is no information on the use of Letairis in patients with mild pre-existing impaired liver function; however, exposure to ambrisentan may be increased in these patients. Elevation of Liver Transaminases: Other endothelin receptor antagonists (ERAs) have been associated with transaminase elevations (AST, ALT) and hepatoxicity, and cases of liver failure (see Adverse Reactions). In patients with VOD undergoing hepatic impairment after Letairis initiation, the cause of liver injury should be fully investigated. Discontinue Letairis if transaminase elevations >5x ULN or if elevations are accompanied by bilirubin >2x ULN, or by signs or symptoms of liver dysfunction. Patients should be educated on the symptoms of potential liver injury (such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant abdominal discomfort, jaundice, dark urine or itching) and instructed to report any of these symptoms to their physician. Hematologic Change: Patients should be advised of the importance of hemoglobin testing. Administration: Patients should be advised not to split, crush, or chew tablets.

For detailed information, please see full prescribing information. To learn more: call 1-800-GILEAD-5 (Option 2) or visit www.letairis.com. For detailed information, please see full Prescribing Information.
Program Announcement:

New Application Deadline: June 12, 2014
Resubmission Deadline: March 12, 2014
New Application Deadline: October 12, 2014
Resubmission Deadline: July 12, 2014

Jointly Sponsored

Mentored Clinical Scientist Development Award (K08) &
Mentored Patient-Oriented Research Career Development Award (K23)

PURPOSE: K08
• To support the development of outstanding clinician research scientists in the area of pulmonary hypertension.
• To provide specialized study for clinically trained professionals who are committed to a career in research in pulmonary hypertension and have the potential to develop into independent investigators.
• To support a 3 to 5 year period of supervised research experience that integrates didactic studies with laboratory or clinically based research.
• To support research that has both intrinsic research importance and merit as a vehicle for learning the methodology, theories, and conceptualizations necessary for a well-trained independent researcher.

MECHANISM:
Awards in response to the program announcement will use the National Institutes of Health (NIH) K08 or the K23 mechanism.

FUNDING:
The award will be funded by PHA and NHLBI and the K08 and/or the K23 will be awarded in 2013.

PURPOSE: K23
• To support career development of investigators who have made a commitment to focus their research endeavors on patient-oriented research.
• To support a 3 to 5 year period of supervised study and research for clinically trained professionals who have the potential to develop into productive, clinical investigators focusing on patient-oriented research in pulmonary hypertension.
• To support patient-oriented research, which is defined as research conducted with human subjects (or on material of human origin, such as tissues, specimens, and cognitive phenomena) for which an investigator directly interacts with human subjects.
• To support areas of research that include: 1) mechanisms of human disease; 2) therapeutic interventions; 3) clinical trials; and 4) development of new technologies.

FOR MORE INFORMATION:
Visit: www.PHAssociation.org/MedicalProfessionals/Research

* Restrictions apply. Please see complete announcement at the website listed above.
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Pulmonary Hypertension Association (PHA) National Heart, Lung, and Blood Institute (NHLBI)

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